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Contribution of 18 F-fluorocholine PET-CT to the preoperative localisation of parathyroid adenoma for the treatment of primary hyperparathyroidism

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18 F-fluorocholine PET-CT is considered a second-line method for the preoperative localisation of parathyroid adenomas in primary hyperparathyroidism. The aim was to compare the diagnostic performance of 18 F-fluorocholine PET-CT and standard imaging modalities in the preoperative localisation of parathyroid adenomas in primary hyperparathyroidism. The primary objective was to assess the performance of 18 F-fluorocholine PET-CT in cases of negative or discordant standard imaging. The secondary objective was to evaluate the diagnostic performance of both 18 F-fluorocholine PET-CT and standard imaging in relation to patient characteristics. We conducted a retrospective, monocentric study, including 156 patients who underwent parathyroidectomy between 2017 and 2023. All patients underwent preoperative 18 F-fluorocholine PET-CT and had an indication for surgery due to primary hyperparathyroidism. A total of 156 patients were included in the study, the majority of whom were women (78%). Seven patients had multigland disease (4.49%). Sensitivity was 60.14% for cervical ultrasound, 46.21% for [99mTc]-MIBI scintigraphy, and 95.97% for 18 F-Fluorocholine PET-CT. 18 F-Fluorocholine PET-CT showed a higher sensitivity than cervical ultrasound and [99mTc]-MIBI scintigraphy, especially for multiple parathyroid adenomas (100, 57.14, and 42.86%, respectively). Univariate analysis showed better results for cervical ultrasound in men ($p = 0.005$). Larger adenomas showed better performance on [99mTc]-MIBI scintigraphy ($p = 0.026$), and elevated PTH levels were associated with significantly worse performance on 18 F-fluorocholine PET-CT ($p = 0.023$). Multivariate analysis showed that scintigraphy performance was worse in the presence of thyroid nodules ($p = 0.049$, RR = 2.046, 95% CI 1.005–4.166). 18 F-fluorocholine PET-CT is a valuable imaging modality for the preoperative localisation of parathyroid adenomas in primary hyperparathyroidism, with superior performance compared to conventional imaging modalities. [99mTc]-MIBI scintigraphy showed reduced diagnostic performance in the presence of thyroid nodules.

Keywords 18F-Fluorocholine PET-CT, Parathyroid adenoma, Primary hyperparathyroidism, Parathyroid scintigraphy.

Primary hyperparathyroidism is a common endocrine disorder, affecting 233 per 100,000 women and 85 per 100,000 men, respectively[1]. It is characterised by excessive production of parathyroid hormone (PTH), mainly caused by a benign tumour of the parathyroid gland called a parathyroid adenoma (85–96% of cases). Less commonly, it is caused by hyperplasia of one or more glands (4–15% of cases)[2], and in very rarely by parathyroid carcinoma (< 1% of cases)[3]. Most patients are asymptomatic, but the condition can lead to renal, or musculoskeletal complications[3]. Surgery remains the primary curative treatment, with the aim of removing the abnormal parathyroid gland. Preoperative localisation is essential as parathyroid adenomas are usually non-

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palpable and can be difficult to locate during surgery. Surgical decisions are based on several criteria outlined in the 2022 International Recommendations[1].

The currently recommended preoperative imaging modalities for primary hyperparathyroidism are cervical ultrasound, [99mTc]-MIBI/[123I] subtraction scintigraphy, and contrast-enhanced 4D-CT[1]. Some international guidelines still do not mention 18 F-fluorocholine PET-CT for preoperative evaluation of primary hyperparathyroidism[1], whereas the European Association of Nuclear Medicine suggests it as a possible first-line imaging modality. When initial imaging is negative or inconclusive, several alternatives have been investigated for preoperative use. The primary aim is to reduce the extent of exploration and minimise surgical failure, which favours minimally invasive parathyroidectomy[4]. These alternatives include cervical ultrasound of the parathyroid gland performed by trained physicians, [99mTc]-MIBI scintigraphy with different modalities (single-photon emission computed tomography [SPECT] combined with CT), 4D-CT, MRI, and 18 F-fluorocholine PET-CT, selective arteriography, selective venous sampling, and cytology with PTH measurement[3,4]. A 2024 study found varying sensitivities for ultrasound, [99mTc]-MIBI SPECT, [99mTc]-MIBI SPECT/CT, and 18 F-fluorocholine PET-CT, with values of 47%, 49%, 71.7%, and 97%, respectively[5], highlighting the variability in diagnostic performance between studies.

PET imaging can be combined with multiple radiotracers (11 C-methionine, 11 C-choline, 18 F-choline) and combined with CT (PET-CT) or MRI (PET-MRI). One of the first studies on the use of 18 F-fluorocholine PET-CT for parathyroid imaging was conducted by Michaud in 2014[6], which demonstrated high accuracy in resolving discordant results between cervical ultrasound and scintigraphy, with a per-patient detection rate of 92% per patient. More recent studies have confirmed the superior diagnostic performance of 18 F-fluorocholine PET-CT over conventional imaging modalities, with a sensitivity of 92% compared with 39–56% for conventional imaging[2]. A 2021 meta-analysis suggests the superiority of 18 F-fluorocholine PET-CT over all other imaging modalities[7]. The first meta-analysis specifically comparing the diagnostic accuracy of 11 C-methionine and 18 F-fluorocholine PET for parathyroid localisation in patients with primary hyperparathyroidism suggests superior performance of 18 F-fluorocholine in terms of sensitivity, while both tracers had comparable accuracy in terms of positive predictive value[8].

18 F-fluorocholine PET-CT has favourable diagnostic characteristics in patients with multigland disease, with good sensitivity (79% for lesion-based analysis, 100% for patient-based analysis) and negative predictive value (NPV) (63% vs. 89% for solitary adenoma detection)[9].

Several predictive factors for imaging failure with first-line modalities were identified that may favour the use of 18 F-fluorocholine PET-CT. These factors include low ionised calcium and PTH levels ($p < 0.001$), small adenoma size, multi-gland disease, coexisting thyroid pathology ($p = 0.018$), and negative ultrasound ($p < 0.001$)[5,9,10]. Cervical ultrasound is operator dependent and has difficulty differentiating parathyroid adenomas from cervical lymph nodes, as well as ectopic parathyroid glands located in the upper mediastinum[9]. Diagnostic performance is reduced for small adenomas, multi-gland disease, upper quadrant adenomas, thyroid hypertrophy (goiter or large nodules), and ectopic parathyroid adenomas (particularly in the thoracic region)[4].

Several studies have shown promising results supporting the use of 18 F-fluorocholine PET-CT in the localisation of parathyroid glands[5,7,11–19].

To our knowledge, no studies have evaluated the diagnostic performance of 18 F-fluorocholine PET-CT based on patient characteristics. One study found a sensitivity of 100% (95% CI: 87.99–100) and a PPV of 85.7% (95% CI: 70.77–94.06) for 18 F-fluorocholine PET-CT, with similar values observed in patients with chronic thyroiditis, nodular goiter, and those who had undergone unsuccessful parathyroid surgery[20]. Excellent diagnostic accuracy for 18 F-fluorocholine PET-CT has also been reported despite the presence of thyroid nodules[21], with patient-based sensitivity > 90% and lesion-based sensitivity > 87%, even in 43% of patients with multinodular goiter or associated thyroid nodules. A review of six studies also found high sensitivity for 18 F-fluorocholine PET-CT (90 to 91.7%) even in the presence of coexisting nodular goiter[22].

The primary objective of this study was to evaluate the performance of 18 F-fluorocholine PET-CT in localising parathyroid glands priori to parathyroidectomy for the treatment of primary hyperparathyroidism, in cases where initial standard imaging was negative or discordant. The secondary objective was to evaluate its performance, as well as that of standard imaging, based on patient characteristics.

Materials and methods

Patients

Patient records were selected from the local Medical Information Department using the CCAM codes "KDFA002", "KDQA001", and "KDFC001". To be included in the study, patients had to have undergone one or more parathyroidectomies at Brest University Hospital between 1 January 2017 and 31 August 2023, be affiliated to a social security system, and be of legal age. Of the 330 patients identified, 166 were excluded because they did not undergo preoperative 18 F-fluorocholine PET-CT. Of the remaining 164 patients, 8 were excluded (4 had multiple endocrine neoplasia type 1 [MEN1], 3 had secondary hyperparathyroidism, and 1 was a minor) [Fig. 1].

No patient was legally protected. A total of 156 patients were retrospectively included in the study. Data collected included demographics (age, sex, BMI), medical history (cervical surgery, parathyroid adenoma), associated thyroid surgery (lobectomy, total thyroidectomy), clinical data (whether hyperparathyroidism was symptomatic or asymptomatic), preoperative and postoperative biological data (calcemia, PTH levels, 24-hour urinary calcium, phosphatemia, vitamin D), and postoperative biological data (calcemia, used to define patient recovery if normalised). The clinical phenotypes of primary hyperparathyroidism were defined as symptomatic if associated with overt skeletal and renal complications, which may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis, or asymptomatic if without overt symptoms or signs typically detected by biochemical screening[1]. The PTH was measured by a simple blood test in the

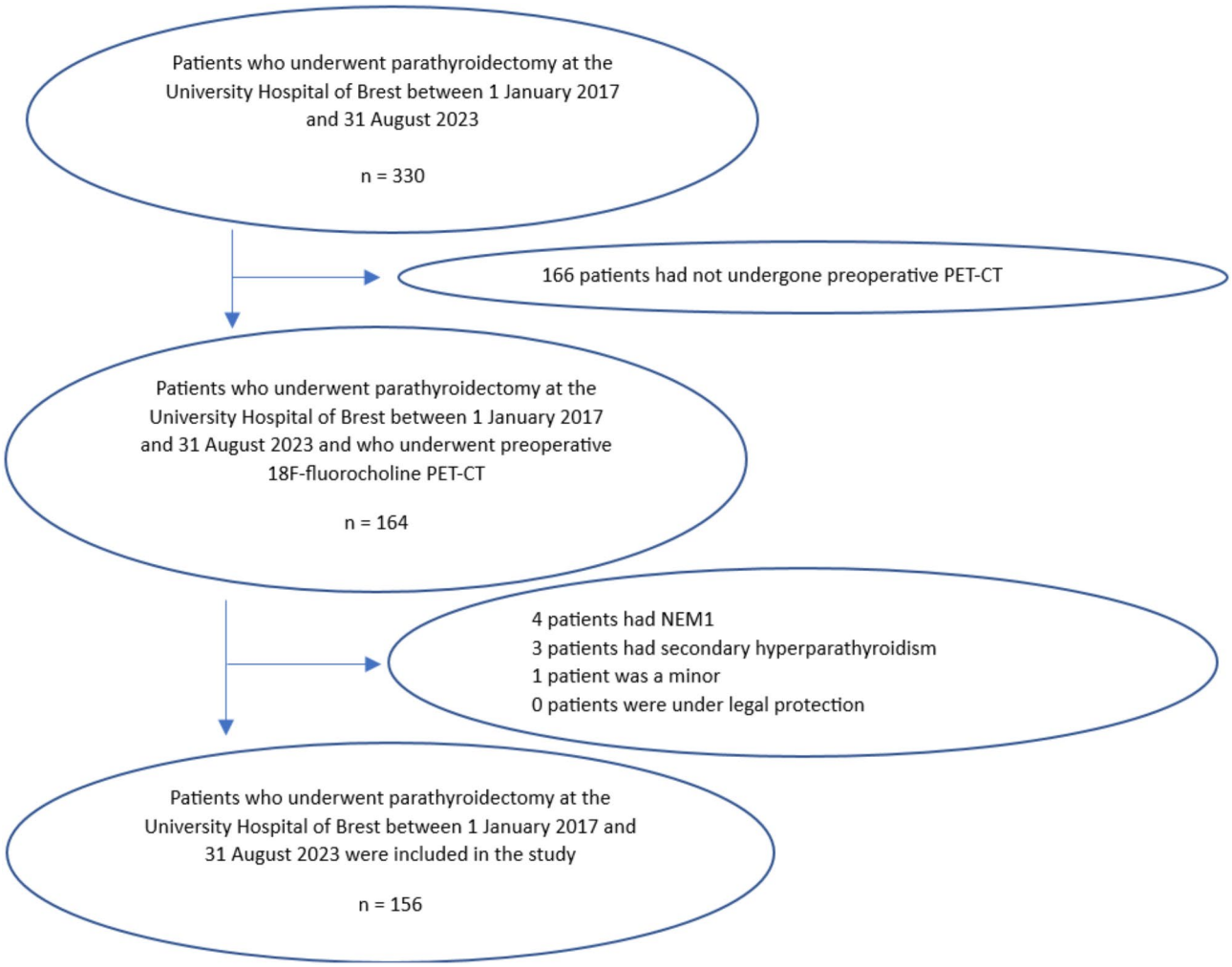

Fig. 1. Flow-chart.

weeks before surgery to help diagnose primary hyperparathyroidism, by using the electrochemiluminescence immunoassay. PTH levels were considered normal if they were between 10 and 65 ng/ml.

Due to the retrospective nature of the study, the need to obtain the informed consent was waived by the Ethics Committee of the University Hospital of Brest – B2023CE.49 –, which approved this study. Patients who did not object to the use of their data were included. All methods were carried out in accordance with relevant guidelines and regulations.

Imaging

Most patients ($n = 142$) underwent two preoperative imaging studies: cervical ultrasound ($n = 155$) and [99mTc]-MIBI scintigraphy ($n = 142$). These were inconclusive, prompting the use of 18 F-fluorocholine PET-CT. The [99mTc]-MIBI scintigraphy included anterior planar images of the neck and thorax 15 min and 3 h after sestamibi-Tc 99 m injection, followed by complementary SPECT images combined with non-contrast CT at 15 min. 18 F-fluorocholine PET-CT imaging of the neck and upper mediastinum was performed 60 min after intravenous administration of 1.5 MBq/kg of fluorocholine radiotracer, while MIBI SPECT/CT imaging of the neck and upper mediastinum followed a two-phase protocol.

Data collected included imaging dates, lesion size when available, location (lateral and superior/inferior positions, or ectopic positions), and presence of thyroid nodules observed on cervical ultrasound.

In the majority of patients (87%, $n = 135$), investigations started with ultrasound, followed by scintigraphy and then PET-CT. The mean time between ultrasound and PET-CT was 158 days [0-1381], between PET-CT and surgery 151 days [2-665], and between ultrasound and surgery 299 days [58-1530].

Gland localisation data obtained from imaging were compared with intraoperative findings and final histopathological analysis. Patients were divided into four categories:

- True negative: no pathological parathyroid gland detected by imaging and no parathyroid adenoma detected by histopathology.

- False negative: no pathological parathyroid gland detected by imaging, but one or more adenomas detected by histopathology.
- False positive: one or more pathological parathyroid glands identified on imaging, but no adenoma identified on histopathology (either no lesion visualised on histopathology or a diagnosis other than parathyroid adenoma).
- True positive: one or more pathological parathyroid glands identified by imaging, and one or more adenomas confirmed by histopathology.

Patients with multiglandular disease were defined by definitive histological analysis showing the presence of parathyroid adenomas in more than one parathyroid gland sampled at surgery. In case of discordant imaging results based on the analysed parathyroid gland, the patient was classified as :

- True positive: at least one pathological parathyroid gland was correctly identified by imaging, and more than one adenoma confirmed by histopathology.
- True negative: no pathological parathyroid gland detected by imaging, and no parathyroid adenoma detected by histopathology.
- False positive: one or more parathyroid glands identified on imaging, but no adenoma identified on histopathology (without pathological parathyroid gland correctly identified by imaging).
- False negative: no pathological parathyroid gland detected by imaging, but one or more adenomas detected by histopathology (without pathological parathyroid gland correctly identified by imaging).

Given the small number of patients with multiglandular disease, the results supporting the good performance of PET-CT did not seem to have a significant impact on the overall results.

Surgical procedure

All patients underwent surgery under general anaesthesia. Each operation was performed with intraoperative monitoring of the recurrent laryngeal nerves. Surgical data collected included the date of surgery, whether the exploration of the parathyroid areas was unilateral or bilateral, the intraoperative localisation of the lesions, the results of the rapid histological examination results, and the final histopathological findings, including lesion size and volume.

Statistical analysis

Several parameters were calculated for each imaging modality: sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy (imaging performance). The effectiveness of each imaging modality was assessed by univariate analysis according to several factors (age, BMI, history of cervical surgery, presence of associated thyroid nodules, adenoma size, preoperative calcium levels, and PTH). Regarding the univariate analyses, Fisher's exact test was used for qualitative variables (female or male sex, presence or absence of a thyroid nodule, presence or absence of a history of cervical surgery) and the Mann–Whitney test was used for quantitative variables (adenoma volume, calcemia, PTH, age, BMI). Bivariate logistic regression was used for criteria with $p < 0{,}15$. A Spearman test was used to study the relationship between vitamin D levels and imaging performance. Statistical analyses were performed using SPSS v25 (IBM Corp, Armonk, NY), with p values < 0,05 considered statistically significant.

Results

Patient characteristics

The characteristics of the patients included in the study are shown in [Table 1]. The mean age was 63 years, with a predominance of women (78%). Most patients were overweight, with an mean BMI of 26.81 kg/m^2. The number of operations increased over time. Most patients were asymptomatic (53%). Osteoporosis was the most common symptom. Seventy-six patients had normal or below threshold calcium levels for surgical indication. All patients underwent surgery, including those with normocalcaemia and high or normal PTH on treatment. One patient did not meet surgical criteria but had a history of resected pulmonary neoplasia. Multiglandular disease was found in 7 patients (4.49%).

Age, BMI, year of surgery, preoperative biological data, and adenoma volume are presented as mean (standard deviation), whereas gender and symptoms are presented as number (percentage). Calcium levels were considered normal if between 2.2 and 2.6 mmol/L. PTH levels were considered normal if between 10 and 65 ng/mL.

In total, of the 156 patients operated on: 147 had parathyroid adenomas, including 140 with a single adenoma and 7 with multiple adenomas; 2 had thyroid carcinoma; 4 had non-pathological parathyroids; one specimen corresponded to lymphoid tissue; and 2 patients had hyperplastic tissue. Analysis of parathyroid localisation performance per patient.

Analysis in parathyroid localisation performance per patient

Among the 156 patients, the sensitivity and PPV for parathyroid adenoma localisation were 60.14 and 88.30% for cervical ultrasound, 46.21 and 92.42% for [99mTc]-MIBI scintigraphy, and 97.95% and 95.97% for 18 F-fluorocholine PET-CT, respectively [Table 2]. The combination of ultrasound and scintigraphy resulted in a sensitivity of 80.1% and a PPV of 98.3%. When ultrasound was performed after PET-CT, the sensitivity was 63%.

Of the 156 patients, we only had 25OH vitamin D levels for 43 patients, including 27 with vitamin D deficiency < 30 ng/ml and 16 with a 25OH vitamin D level ≥ 30 ng/ml. In these 43 patients, we found no

Characteristics	Data
Age (years)	63.21 (11.61)
Gender	
Male	34 (21.79)
Female	122 (78.21)
BMI (kg/m²)	26.81 (6.64)
Year of surgery	2020.53 (1.74)
Corrected calcium (mmol/l)	2.77 (0.21)
PTH (pg/ml)	143.35 (122.52)
Asymptomatic	82 (52.56)
Symptomatic	74 (47.44)
Neuropsychological	1 (0.64)
Nephrological	39 (25)
Rheumatological	67 (42.95)
Cardiovascular	4 (2.56)
Multiglandular disease	7 (4.49)
Adenoma volume (mm³)	1071 (912)

Table 1. Characteristics of patients enrolled in the study.

Analysis per patient	Ultrasound *n* = 155	Scintigraphy *n* = 142	Ultrasound + Scintigraphy *n* = 142	PET-CT *n* = 156
Sensitivity (%)	60.14	46.21	80.1	97.95
Specificity (%)	35.29	50	78.8	40
PPV (%)	88.30	92.42	98.3	95.97
NPV (%)	9.84	6.58	19.4	57.14
Accuracy (%)	57	46	79.5	94.2

Table 2. Intrinsic (sensitivity, specificity) and extrinsic (PPV, NPV) performance, and accuracy of imaging modalities for parathyroid localisation, independent of final histopathological analysis.

significant correlation between vitamin D levels and imaging performance, with p-values of 0.821, 0.575, and 0.220 for ultrasound, scintigraphy, and PET, respectively.

Performance analysis in multiglandular disease

In patients with a single adenoma confirmed by final histopathological analysis, the sensitivity was 60% for cervical ultrasound, 45.97% for [99mTc]-MIBI scintigraphy, and 97.83% for 18 F-fluorocholine PET-CT. False negatives included 52 glands for cervical ultrasound, 67 for [99mTc]-MIBI scintigraphy, and 3 for 18 F-fluorocholine PET-CT. False positives results were 6.47% (9 glands) for cervical ultrasound, 2.36% (3 glands) for [99mTc]-MIBI scintigraphy, and 1.43% (2 glands) for 18 F-fluorocholine PET-CT. In the 7 patients with multiglandular disease, the sensitivity was 57.14% for cervical ultrasound, 42.86% for [99mTc]-MIBI scintigraphy, and 100% for 18 F-fluorocholine PET-CT. All 18 F-fluorocholine PET-CT images corresponded to adenomas in the final histopathological analysis.

Performance analysis in patients with previous cervical surgery

In patients with no history of prior cervical surgery, the sensitivity was 60.53, 43.12, and 97.5% for cervical ultrasound, [99mTc]-MIBI scintigraphy, and 18 F-fluorocholine PET-CT, respectively. In patients with a history of cervical surgery, sensitivity was 56.25%, 66.67%, and 100% for cervical ultrasound, [99mTc]-MIBI scintigraphy, and 18 F-fluorocholine PET-CT, respectively.

Performance analysis in overweight or obese patients

In patients with a BMI < 25 kg/m², the sensitivity was 60.61% for cervical ultrasound, 48.57% for [99mTc]-MIBI scintigraphy, and 98.65% for 18 F-fluorocholine PET-CT. In overweight patients with a BMI ≥ 25 kg/m², the sensitivity was 61.54% for cervical ultrasound, 42.11% for [99mTc]-MIBI scintigraphy, and 97.01% for 18 F-fluorocholine PET-CT.

Performance analysis in patients with associated thyroid nodules

In patients without associated thyroid nodules, the sensitivity was 61.90, 50, and 100% for cervical ultrasound, [99mTc]-MIBI scintigraphy, and 18 F-fluorocholine PET-CT, respectively. In patients with thyroid nodules, the sensitivity was 58.75%, 40%, and 97.59% for cervical ultrasound, [99mTc]-MIBI scintigraphy, and 18 F-fluorocholine PET-CT, respectively.

	Male (%)	Female (%)	*p*	No nodule (%)	Nodule (%)	*p*	No cervical surgery (%)	Cervical surgery (%)	*p*
Ultrasound	79	52	0.005	57	58	0.954	58	50	0.498
Scintigraphy	56	45	0.113	55	40	0.096	44	62	0.194
Ultrasound + Scintigraphy	97	76	0.009	87	76	0.091	80	83	0.748
PET	94	94	0.97	92	96	0.361	93	100	0.250

Table 3. Imaging accuracy for parathyroid adenoma localisation per patient based on sex, presence of associated thyroid nodules, and history of cervical surgery.

p	Adenoma volume	Calcemia	PTH	Age	BMI
Ultrasound	0.851	0.473	0.628	0.159	0.991
Scintigraphy	0.026	0.958	0.247	0.126	0.304
Ultrasound + Scintigraphy	0.133	0.353	0.984	0.964	0.685
PET	0.607	0.880	0.023	0.681	0.325

Table 4. Univariate analysis of imaging accuracy for parathyroid adenoma localisation according to patient characteristics.

Scintigraphy	*p*	RR	95% CI
Female sex	0.068	0.950	0.899–1.004
Thyroid nodule	0.049	2.046	1.005–4.166
Age	0.070	1.028	0.998–1.060
Constant	0.490	0.427	

Table 5. Multivariate analysis of the accuracy of [99mTc]-MIBI scintigraphy for parathyroid localisation per patient.

In patients without thyroid nodules, the combined sensitivity and PPV of ultrasound and [99mTc]-MIBI scintigraphy were 85% and 100%, respectively, whereas 18 F-fluorocholine PET-CT had a sensitivity of 98.3% and a PPV of 94%.

Univariate analysis of imaging performance based on baseline patient characteristics

Cervical ultrasound performed better in localising parathyroid adenomas in men ($p = 0.005$) [Table 3]. This finding was also true for the combination of ultrasound and scintigraphy ($p = 0.009$). There was no statistically significant difference for other parameters, including the presence or absence of thyroid nodules on [99mTc]-MIBI scintigraphy ($p = 0.084$).

The larger the adenoma, the better the performance of [99mTc]-MIBI scintigraphy (p = 0.026) [Table 4]. When PTH levels were elevated, the performance of 18F-fluorocholine PET-CT performance was significantly lower (p = 0.023). Using a PTH cut-off of 200 pg/ml, the efficacy was 96% for PTH < 200 pg/ml compared to 81% for PTH > 200 pg/ml. In this situation of very high PTH, the combination of cervical ultrasound and [99mTc]-MIBI scintigraphy had an effectiveness of 94%, although not significantly better (p = 0.6). No other statistically significant differences were found for the other parameters.

Multivariate analysis of imaging performance based on secondary criteria

Multivariate analysis of the diagnostic performance of [99mTc]-MIBI scintigraphy, according to the three secondary parameters with a $p < 0.15$ in univariate analysis, showed a statistically significant difference, with poorer diagnostic performance in the presence of a thyroid nodule compared to other imaging modalities ($p = 0.049$, RR = 2.046, 95% CI 1.005–4.166) [Table 5]. As only one criterion was significant, multivariate analyses were not performed for ultrasound and 18 F-fluorocholine PET-CT.

Discussion

The intrinsic performance observed in our study, with sensitivities of 60.14, 46.21, and 97.95%, respectively, for cervical ultrasound, [99mTc]-MIBI scintigraphy, and 18 F-fluorocholine PET-CT, and PPVs of 88.30, 92.42, and 95.97%, is in good agreement with the literature. A meta-analysis[23] of 18 studies reported a sensitivity of 95% and a PPV of 97% for 18 F-fluorocholine PET-CT. A retrospective observational study between 2018 and 2021 comparing 18 F-fluorocholine PET-CT with conventional imaging showed better parameters (overall lesion detection increased to 97.9%, and there was a significant reduction in parathyroid adenoma localisation failure from 11.34 to 2.06%, $p < 0.05$)[16]. Thus, 18 F-fluorocholine PET-CT appears to offer superior sensitivity and diagnostic accuracy.

For multiple parathyroid adenomas, the sensitivity of 18 F-fluorocholine PET-CT was higher than that of cervical ultrasound and [99mTc]-MIBI scintigraphy, at 100, 57.14, and 42.86%, respectively. The literature shows that 18 F-fluorocholine PET-CT identified 9 parathyroid adenomas that were missed by [99mTc]-MIBI/[123I] subtraction scintigraphy in 8 of 64 patients (12.5%), detecting 4 patients with multiglandular disease and one ectopic gland[24]. Wolf's study reported a lower sensitivity for [99mTc]-MIBI SPECT/CT in multiglandular disease compared to single gland disease, with detection rates of 45% versus 60%[11]. It also found a significant correlation between accurate adenoma localisation and 18 F-fluorocholine PET-CT as preoperative imaging ($p < 0.01$), with detection rates of 11%, 30%, and 83% for ultrasound, [99mTc]-MIBI SPECT/CT, and 18 F-fluorocholine PET-CT, respectively. Futhermore, preoperative ultrasound and scintigraphy results appear to be predictive of multiglandular disease, with a 31.6% risk of multiple adenomas in cases with negative imaging compared to 3.6% in cases with positive imaging[4].

In our study, factors such as weight, previous neck surgery, or associated thyroid nodules did not seem to affect the performance of 18 F-fluorocholine PET-CT, which might otherwise interfere with image interpretation and alter its intrinsic parameters. Contrary to the literature, univariate analysis showed no significant difference with [99mTc]-MIBI scintigraphy in the presence or absence of thyroid nodules (55% sensitivity without nodules and 40% with nodules, $p = 0.084$), although nodules may obscure parathyroid gland localisation. Some nodular goiters show higher 99mTc-MIBI uptake, making differentiation from hyperactive parathyroid lesions difficult. Meanwhile, the presence of a thyroid nodule did not affect the diagnostic performance of ultrasound ($p = 0.954$), although coexisting thyroid disease may reduce the performance of both [99mTc]-MIBI scintigraphy and ultrasound[25]. The high prevalence of multinodular goiter or thyroid nodules (43%) partly explains the high negative rate imaging with [99mTc]-MIBI SPECT/CT and/or ultrasound[21], while the diagnostic accuracy of 18 F-fluorocholine PET-CT remains unchanged.

In our study, 18 F-fluorocholine PET-CT remained more sensitive (98.3%) than the combination of ultrasound and [99mTc]-MIBI scintigraphy (85%) in patients without thyroid nodules, overcoming a major limitation of scintigraphy. In addition, multivariate analysis showed that scintigraphy had significantly worse diagnostic performance in the presence of a thyroid nodule ($p = 0.049$, RR = 2.046, 95% CI 1.005–4.166). Thus, it may be beneficial to consider 18 F-fluorocholine PET-CT as a first-line imaging modality when a thyroid nodule is detected by ultrasound, without performing scintigraphy. The sensitivity of 18 F-fluorocholine PET-CT in patients with prior neck surgery was superior to conventional imaging (100% vs. 56.25% for ultrasound and 66.67% for [99mTc]-MIBI scintigraphy), a finding consistent with the literature. In patients who had previously undergone cervical surgery, the sensitivity for localising parathyroid adenomas was 85.2, 63.2, 46.2, and 48.0% for 18 F-fluorocholine PET-CT, 4D-CT, cervical ultrasound, and [99mTc]-MIBI scintigraphy, respectively[26]. In this group, abnormal glands were removed in 21 patients, 12 of whom had negative or discordant [99mTc]-MIBI scintigraphy and ultrasound results. Surgery of the neck results in scarring and anatomical changes that complicate the detection of abnormal parathyroid glands[10]. 18 F-fluorocholine PET-CT therefore appears useful in the management of patients with persistent and/or recurrent hyperparathyroidism when first-line scintigraphy is negative[27].

In patients with elevated PTH levels (> 200 pg/ml), the performance of 18 F-fluorocholine PET-CT was worse (81%) compared to cases with lower PTH levels (96%, $p = 0.023$). Given the small number of patients with high PTH levels ($n = 16$), this may represent a sampling bias, and it would be useful to investigate this observation in larger cohorts.

Ultrasound performed after PET-CT may be better due to bias in the initial results; however, the sensitivity in our study remained similar at 63% for ultrasound performed before PET-CT and 60% for all combined ultrasounds.

The specificity of PET-CT was 40% in our study, which is lower than in the literature. However, the results refer to all patients, including those without parathyroid adenoma confirmed by definitive pathological analysis. In fact, we found a total of six false positives with F-PET-CT, including two parathyroid adenomas (mislocalisation), one lymph node, two hyperplastic tissues and one tissue without abnormality. Because of the higher number of false positives, and a low proportion of false negatives ($n = 3$), the overall specificity calculated in our study was lower than that corresponding only to patients with a single parathyroid adenoma, and therefore lower than that reported in the literature.

The number of operations in our study increased over time, probably due to the increasing use of PET-CT, reflecting its growing progress. However, access to this imaging modality can be difficult in France, depending on geographical location, and its high cost poses significant medico-economic challenges. According to the Common Classification of Medical Acts (CCAM), a transcutaneous ultrasound of the parathyroid glands costs €37.80, while parathyroid scintigraphy costs €268.87. 18 F-fluorocholine PET/CT, including the contrast agent, costs €881[28]. Its use remains limited in France for economic reasons, as all PET/CT scans are currently reimbursed similarly regardless of the tracer used (making their cost identical from a health insurance perspective), although hospital production costs vary. A European health economic evaluation compared 18 F-fluorocholine PET/CT as a first-line imaging modality with the current standard of care, where 18 F-fluorocholine PET/CT is recommended only after a negative or equivocal [99mTc]-MIBI SPECT/CT. This analysis found that long-term simulated costs were similar for both imaging strategies, suggesting that they can be used interchangeably[29].

Our study has several limitations. It is a retrospective, single centre study, which limits the external validity and generalisability of the results. The performance of MIBI and US are undoubtedly underestimated considering that the sample included only patients who needed a subsequent 18 F-fluorocholine PET-CT. Besides, the study population included a high proportion of women, which introduces a selection bias, but this is to be expected given that primary hyperparathyroidism predominantly affects women. The number of patients with multiglandular disease was limited to 7, making it difficult to draw conclusions about this criterion. In addition, the same PET/CT scanner was used for most patients, so it would be interesting to evaluate the diagnostic

performance based on different models, including those for scintigraphy and cervical ultrasound. In addition, there is likely to be variability in results depending on the ultrasound operator.

The main strength of this study is the large number of included patients included compared with other studies in the literature, which makes it easier to apply to everyday clinical practice.

Conclusion

Our study demonstrates the superiority of 18 F-fluorocholine PET-CT in the preoperative localisation of parathyroid adenomas in patients with primary hyperparathyroidism undergoing surgery, particularly in cases where conventional imaging gives discordant results. The sensitivity was 60.14% for cervical ultrasound, 46.21% for [99mTc]-MIBI scintigraphy, and 97.95% for 18 F-fluorocholine PET-CT. The PPV was 88.30% for ultrasound, 92.42% for [99mTc]-MIBI scintigraphy, and 95.97% for 18 F-fluorocholine PET-CT.

Multivariate analysis of different factors showed that [99mTc]-MIBI scintigraphy had significantly lower diagnostic performance in the presence of thyroid nodules ($p = 0.049$, RR = 2.046, 95% CI 1.005–4.166). Therefore, if access to 18 F-fluorocholine PET-CT is limited, it should be preferred in patients with associated thyroid pathology.

Data availability

All data generated or analyzed during this study are included in this articles. Further enquiries can be directed to the corresponding author.

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Declarations

Competing interests
The authors declare no competing interests.

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