Value of [^{11}C]-Methionine PET/CT in Preoperative Localization of Parathyroid Adenomas

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Key words

primary hyperparathyroidism, subtraction scintigraphy, ultrasound, 4-dimensional computed tomography

received 16.09.2020
accepted after revision 22.03.2021
published online 24.06.2021

Bibliography

Horm Metab Res 2021; 53: 444–452
DOI 10.1055/a-1475-4600
ISSN 0018-5043

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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ABSTRACT

There are multiple imaging modalities in primary hyperparathyroidism. Ultrasound examination and subtraction scintigraphy are usually the first-line imaging techniques. When these results are negative or inconsistent, additional [^{11}C]-methionine PET/CT (MET-PET/CT) or 4-dimensional computed tomography can be performed. This study aims to evaluate MET-PET/CT in comparison with other imaging techniques in primary hyperparathyroidism. This is a retrospective cohort study. Eighty-four patients with primary hyperparathyroidism, who underwent parathyroid surgery, were included. Imaging results have been correlated to the perioperative drop in parathyroid hormone level and to the pathological analysis. Descriptive statistics are used, supplemented with 95 % Clopper–Pearson confidence intervals for sensitivity and specificity and a sub-analysis with the McNemar test on paired data only. The per-lesion sensitivity of MET-PET/CT seems higher than that of [^{99m}Tc]-sestamibi or [^{99m}Tc]-tetrofosmin and [^{99m}Tc]-pertechnetate subtraction scintigraphy. The McNemar test, on paired data only, shows significantly higher sensitivity of MET-PET/CT compared to ultrasound ($p = 0.039$) and significantly higher specificity of ultrasound compared to subtraction scintigraphy ($p = 0.035$). MET-PET/CT after inconclusive or negative ultrasound and/or subtraction scintigraphy has an additional value in 70 % of the cases. Preoperative parathyroid hormone levels were higher in patients in whom MET-PET/CT correctly predicted the pathological parathyroid glands, compared to those where MET-PET/CT missed at least one adenoma. The same trend was seen for 4-dimensional computed tomography. In conclusion, MET-PET/CT seems a valuable imaging modality in primary hyperparathyroidism, at least as second line imaging approach, with a higher per-lesion sensitivity than ultrasound in such setting. Especially when ultrasound and/or subtraction scintigraphy are inconclusive or negative, MET-PET/CT directs the surgeon to the correct localization of the parathyroid adenoma.

Introduction

In primary hyperparathyroidism (PHPT) a correct preoperative localization of the parathyroid adenoma(s) (PA) is crucial. Multiple imaging modalities can be used to guide the surgeon. Ultrasound examination (US) and subtraction scintigraphy are used typically as first-choice techniques. When these are negative or inconclusive, a [^{11}C]-methionine positron emission tomography-computed tomography (MET-PET/CT) or a 4-dimensional computed tomography (4D-CT) can be used as complementary detection methods.

PHPT

PHPT has a prevalence of 0.1–0.9 %, which makes it the third most common endocrinological disease, after diabetes, and hypothyroidism [1, 2]. More women are affected than men with a ratio of

2.5–4:1 [2–4]. PHPT is diagnosed by increased parathyroid hormone (PTH) levels, which are inappropriately high compared to the hypercalcemia after exclusion of secondary hyperparathyroidism [5]. The most important complications of PHPT are nephrolithiasis and bone demineralization, but also pancreatitis, hypertension and neurocognitive impairment can occur [3]. The physician must consider a medical treatment with calcimimetics and/or bisphosphonates or a curative surgical removal of the hypersecreting adenoma(s) to prevent evolution of PHPT with detrimental effects. Treatment is recommended in patients with symptoms, end-organ disease (such as nephrolithiasis, osteoporosis or fragility fractures), young age (< 50 years), an albumin-corrected calcium level of 0.25 mmol/l above the upper limit of normal or a creatinine clearance below 60 ml/min [6, 7].

Ultrasound examination

Ultrasound examination (US) is a widely available, low-cost technique without exposure to ionizing radiation that is often used to visualize the PA. There are, however, known limitations in detecting ectopic adenoma(s) and there is a notable operator-dependence [6]. Per-lesion sensitivity is reported between 58 and 78 % [8–10].

Subtraction scintigraphy

Another well-known technique is subtraction scintigraphy where two tracers are injected: one tracer that is taken up by the thyroid ([^{99m}Tc]-pertechnetate or [^{123}I]) and a second tracer taken up by the thyroid and the parathyroid tissue ([^{99m}Tc]-sestamibi or [^{99m}Tc]-tetrofosmin). Afterward, the images with these tracers are subtracted from each other. The imaging is based on the capture of a single photon, with planar imaging or single-photon emission computed tomography (SPECT). This is in contrast to PET, where every decay results in a double detection, which produces a higher resolution. Up until now subtraction scintigraphy is widely accepted and performed. The sensitivity of this technique is reported to be between 64 and 83 % [9–11].

4D-CT

4D-CT is computed tomography of the parathyroid glands with multiple acquisitions over time (4th dimension) before and after the injection of iodine contrast. Parathyroid adenomas are differentiated from the thyroid tissue and lymph nodes with an earlier peak time and a more rapid wash-in (S. Raeymaeckers, personal communication [12, 13]). This technique is less often used to locate PA, partly because it requires the injection of iodine contrast in this specific population with a higher prevalence of renal toxicity [5, 14]. 4D-CT is more regarded as a second option when US and/or subtraction scintigraphy are negative or inconclusive [13]. The sensitivity is estimated at around 89 % in a systematic review [15].

MET-PET/CT

In 1994, [^{11}C]-methionine was introduced as a new radiopharmaceutical in parathyroid imaging, using stand-alone positron emission tomography (PET) cameras [16]. Before that, [^{11}C]-methionine was already used in visualizing cerebral tumors. This agent was chosen because of its accumulation in abnormal tissue of parathyroid glands (PG) in PHPT, being more specific for parathyroid tissue than the uptake of [^{99m}Tc]-sestamibi compared to the uptake in thyroid tissue, and also because of a superior spatial resolution [17, 18]. Nevertheless, [^{11}C]-methionine is taken up more intensively by cervical soft tissue compared to [^{99m}Tc]-sestamibi. In 2006 PET evolved to PET/CT to correlate the PET-images to the anatomical information, provided by CT [19]. This facilitated the correct identification and localization of PA. MET-PET/CT has already shown to have additional benefits compared to US and/or subtraction scintigraphy in 50–86 % of the patients, especially patients with ectopic adenomas and adenomas near the thyroid that are located at unusual sites (e. g., anterior to the thyroid) [20–22]. The sensitivity of MET-PET/CT is comparable to or better than the sensitivity of subtraction scintigraphy [20, 23]. Per-lesion sensitivity of MET-PET/CT is reported between 70 and 81 % [24–27]. In multiglandular disease (MGD) MET-PET/CT has a lower sensitivity (67 %) than in single adenomas (83 %), with typically only the largest hyperplastic parathyroid gland detected [28]. An explanation for this decrease in sensitivity could be a different physiopathology with less PTH-synthesis and a lower uptake per weight of tissue of [^{11}C]-methionine in hyperplastic glands, compared to PA [20]. The sensitivity of MET-PET/CT after negative or inconclusive subtraction scintigraphy was 86 % in a meta-analysis, evaluated per patient [18]. Given its high sensitivity and specificity, MET-PET/CT is considered a complementary technique in case of discordant or negative US and subtraction scintigraphy [18]. The routine use of MET-PET/CT is mainly limited by the need for a cyclotron nearby due to the short half-life of [^{11}C]-methionine, that is, 20 minutes, and the accompanying high workload for the preparation [29].

[^{18}F]-Fluorocholine PET/CT (FCH-PET/CT)

The uptake of [^{18}F]-fluorocholine into cells happens through a carrier-mediated transport mechanism. Consequently, [^{18}F]-fluorocholine becomes incorporated into the phospholipids of the cell membranes. This happens especially in malignant cells, due to the upregulation of choline kinase (phosphorylation of choline) in these cells with increased proliferation [30]. [^{18}F]-Fluorocholine is most frequently used in imaging of prostate cancer and hepatocellular carcinoma. The first study with this agent for the detection of PA was conducted in 2014, and since then only a small number of studies were conducted with a per-lesion sensitivity of 88–94 % [29, 31–34]. In a systematic review and a meta-analysis, the pooled sensitivity per-lesion and per-patient were respectively 92–94 % and 95–97 % [35, 36]. The half-life of [^{18}F]-fluorocholine is 110 minutes [27]. For patients of the UZ Brussel, this technique was not used, and thus it is not evaluated in this study.

Surgery

Bilateral neck exploration and minimally invasive parathyroidectomy (MIP) are two approaches in parathyroid surgery. The choice between both options is largely based on the experience of the surgeon. For MIP it is very important to know the localization of the PA preoperatively to successfully carry out the intervention. The reduction in operating time, the accelerated recovery, the limited scarring and better pain control postoperatively favor MIP [37]. Yet, even with open surgery knowing the location of the adenomas is advantageous, resulting in reduced operating time and decreased risk to damage the recurrent laryngeal nerve [21].

Aim

The aim of this study is to evaluate the value of MET-PET/CT in preoperative localization of PA in PHPT compared to more known techniques, such as US, subtraction scintigraphy and 4D-CT. This study focusses on the patients of the UZ Brussel, which form a relatively large cohort. In addition, the influence of preoperative laboratory tests on the prediction by the different imaging techniques will be investigated.

Patients and Methods

Patients

In this retrospective study, the medical data of all patients who underwent parathyroidectomy in the UZ Brussel over 10 years (from 01 January 2008 until 31 December 2017) were analyzed. Exclusion criteria were secondary (9 patients) and tertiary hyperparathyroidism (10 patients), multiple endocrine neoplasia (MEN) syndrome (3 patients), chronic kidney disease (CKD) 3B or a more severe grade (according to the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines) (22 patients), incomplete hospital notes (6 patients), known malignancy (5 patients), parathyroid carcinoma (1 patient) and no proof of PA, nor a hyperplastic gland in the pathological analysis (1 patient).

After exclusion, 84 patients with PHPT remained in this cohort. For every patient the following data were collected for further study: gender, age at the time of surgery, preoperative and late-postoperative (between 6 and 12 months after surgery) levels of PTH, calcium, albumin, phosphate and vitamin D, early-postoperative (the evening on the day of the surgery) PTH levels, the results of US, subtraction scintigraphy, MET-PET/CT and 4D-CT and the pathology results. The calcium levels were corrected for the albumin concentration with the following equation: adjusted calcium (mmol/l) = total calcium (mmol/l) − 0.02 (albumin (g/l)–40) [38, 39]. All reported calcemias were corrected for albumin unless stated otherwise. The approval for the data collection and the execution of this study was obtained from the ethical medical committee of the UZ Brussel.

Surgery

All patients underwent open parathyroid surgery in the UZ Brussel, with subsequent analysis of the removed tissue by the pathologists of the UZ Brussel. Before, during and after the removal of the adenoma, PTH was measured to establish a suitable decrease in PTH levels.

Imaging

Most of the imaging studies (US, subtraction scintigraphy and 4D-CT) were performed in the UZ Brussel. As [^{11}C]-methionine is not produced in the UZ Brussel, all patients were referred to the Hôpital Erasme in Brussels for their MET-PET/CT studies. Not every patient underwent every imaging modality due to the retrospective design. ▶ **Figure. 1** shows an example of images from MET-PET/CT.

[^{11}C]-Methionine was injected approximately 20 minutes before imaging was performed. Images were obtained with a Philips Gemini TF TOF 64 PET/CT or Philips Allegro Body.

The images of the subtraction scintigraphy were made with a Philips BrightView XCT SPECT/CT with low-energy collimators from 07 August 2009 onwards. Before this date, subtraction scintigraphy was performed using planar imaging. In 2016, [^{99m}Tc]-sestamibi was replaced by [^{99m}Tc]-tetrofosmin for subtraction scintigraphy, because of its better biodistribution characteristics when used for cardiac imaging.

4D-CT was performed on a GE Healthcare Revolution CT, with single-shot axial scanning. After the performance of a non-enhanced CT, a 90 ml-bolus of iodine-contrast was injected at a velocity of 6 ml/s. At 20 seconds post-injection, 11 acquisitions (with 2 s between each acquisition) were obtained, then was switched to another 4 acquisitions with 10 seconds interval.

For MET-PET/CT and 4D-CT the mean total radiation exposure per patient was calculated with their standard deviations. For subtraction scintigraphy a typical effective dose per patient was computed, since the actual injected values were not registered in the hospital notes for every patient. The period between the performance of imaging and the surgery was collected and reported per imaging technique.

Per-lesion analysis

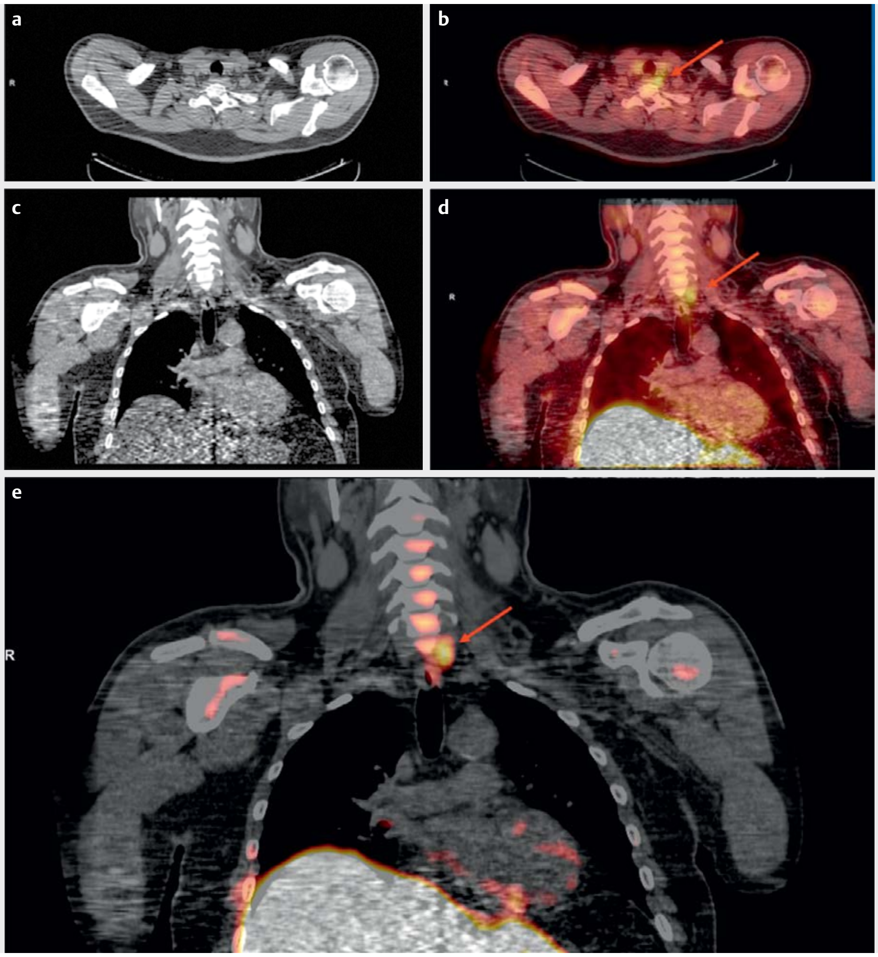
Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated per-lesion. Per study patient, typically 4 PG were assessed, or 5 in case of pathology-proven ectopic PG. All lesions that were either confirmed as adenoma or hyperplastic gland by pathological assessment were considered positive. All other lesions, either not resected or considered as normal PG by pathological assessment, were considered negative. Most PG defined as 'normal PG' were not excised and not evaluated pathologically, nevertheless the remaining PG are assumed to be normal, based on the reduction in perioperative PTH levels. 2 × 2-Tables were constructed with division of the columns in 'adenoma/hyperplastic gland' and 'normal PG', and division of the rows in 'reported as adenoma/hyperplastic gland' and 'not reported as adenoma/hyperplastic gland'.

Preoperative PTH and calcium levels

To focus on the importance of preoperative PTH and calcium levels, the following strategy is followed. For each imaging modality patients have been divided into two groups: true positive (all adenomas have been predicted) and false negative (at least one adenoma was not predicted). Mean PTH levels and boxplots were calculated for every group per imaging modality. The same analyses were made for calcium levels.

Statistics

Predominantly descriptive statistics were used to report the results. 95 % Clopper–Pearson confidence intervals were calculated for the sensitivity and specificity. The decision to perform additional imaging could be influenced by the results of previous imaging, which led to a sampling bias. To handle this bias, a sub-analysis of the imaging results was made on paired data only, using the McNemar test, with an α-value of 5 %. All statistics were performed with IBM SPSS Statistics 23.



▶ **Fig. 1** Imaging of a patient with a parathyroid adenoma on the lower left side using MET-PET/CT. **a** and **c** are CT images; **b** and **d** are PET/CT fusion images showing the increased uptake of [^{11}C]-methionine in the parathyroid adenoma (indicated with the red arrow); **e** is similar to **d** but with background subtraction in the PET overlay image.

Results

Of 121 patients, identified as having undergone a parathyroidectomy between 01 January 2008 and 31 December 2017 in the UZ Brussel, 37 patients were excluded because of the presence of one or more exclusion criteria. Subsequently, 84 patients were available for further analysis in this study. A total of 75 patients (89 %) had a single PA (of which 5 were ectopic adenomas) and 9 patients (11 %) had MGD (4 patients had 2 adenomas, and 5 patients had hyperplasia). The female-to-male ratio was 3:1 in this population, with a mean age of 56 years (SD ± 12 years). These findings are listed in ▶ **Table 1** and are in line with results reported in other studies [2, 27, 40].

Based on the pathological analysis of excised tissue and the perioperative drop in PTH level, a total of 103 adenomas/hyperplastic glands were surgically removed in these 84 patients. The distribution in location of pathological glands is as follows: 20 upper right (19.4 %), 27 lower right (26.2 %), 14 upper left (13.6 %), 1 left in the middle (1.0 %), 36 lower left (35.0 %), and 5 ectopic adenomas (4.9 %). Resected pathological glands were almost equally distributed over left (47) and right (51). In contrast, 63 resected glands were situated on the lower side and only 34 were localized on the upper side of the thyroid.

Hypercalcemia was present in 64 patients (76.2 %). Sixteen patients had normocalcemia (19.0 %), but all of them had elevated PTH levels. In the four remaining patients (4.8 %) no albumin concentration had been measured, but their uncorrected calcium also showed hypercalcemia. In two of the hypercalcemic patients, the preoperative PTH was in the normal range but inappropriately high for their calcium level: a 27-year old woman had hypercalcemia of 2.48 mmol/l (normal range: 2.15–2.45) with nephrolithiasis and a 54-year old woman had hypercalcemia of 2.60 mmol/l (normal range: 2.15–2.45) with osteopenia, suspected nephrolithiasis, and constipation.

Immediately after surgery 37.8 % of the patients had normalized PTH levels and 62.2 % had low PTH levels. The PTH level between 6 and 12 months after the surgery had normalized in 83 % of the patients. 17 % of the patients still had increased levels of PTH (i. e., more than 65 ng/l) of on average 79.7 ng/l (SD ± 19.6 ng/l), but all of them had normalized (87 %) or low (13 %) calcemia between 6 and 12 months after surgery.

Imaging

The injected activity of the [^{11}C]-methionine ranged between 527 MBq and 851 MBq with a mean of 652 MBq (SD ± 90.7), which typically corresponds to a whole body radiation burden of 3.4 mSv [41]. The effective dose of the low-dose CT is estimated at 1.4 mSv [42]. This results in an estimated mean total effective dose of 4.9 mSv for MET-PET/CT. The mean effective dose of 4D-CT was 3.9 mSv (SD ± 1.7 mSv). The images of the subtraction scintigraphy were obtained approximately 15 minutes and 5 minutes after the injection of respectively 74 MBq [^{99m}Tc]-pertechnetate and 740 MBq [^{99m}Tc]-sestamibi/[^{99m}Tc]-tetrofosmin. Together, these tracers typically result in an effective dose of 6.88 mSv per patient. No [^{123}I] was used in this study. The effective dose of the low-dose CT of the subtraction scintigraphy was typically 1.65 mSv. The overall effective radiation dose of subtraction scintigraphy was approximately 8.35 mSv.

The mean time between surgery and imaging (US, subtraction scintigraphy, MET-PET/CT and 4D-CT) was 136 days (SD ± 221 days), 165 days (SD ± 304 days), 63 days (SD ± 38 days), and 55 days (SD ± 45 days), respectively.

▶ **Table 1** Characteristics of the patients.

Mean Age (SD) – years	56 (± 12)
Male sex – no (%)	21 (33)
Localization of the adenoma/hyperplastic gland – no (%)	
Upper right	20 (19.4)
Lower right	27 (26.2)
Upper left	14 (13.6)
Middle left	1 (1.0)
Lower left	36 (35.0)
Ectopic	5 (4.9)
MGD – no (%)	
Double adenoma	4 (4.8)
Hyperplasia	5 (6.0)
Hypercalcemia (corrected for albumin) – no (%)	
High PTH	62 (73.8)
Normal PTH	2 (2.4)
Hypercalcemia (uncorrected for albumin) – no (%)	
High PTH	4 (4.8)
Normocalcemia – no (%)	
High PTH	16 (19.0)
Imaging modality – no (%)	
US	75 (89.3)
Subtraction scintigraphy	62 (73.8)
MET-PET/CT	16 (19.0)
4D-CT	8 (9.5)

SD: Standard deviation; no.: Number; MGD: Multiglandular disease; PTH: Parathyroid hormone; US: Ultrasound; MET-PET/CT: [^{11}C]-Methionine positron emission tomography-computed tomography; 4D-CT: 4-Dimensional computed tomography.

Per-lesion analysis

In all patients, every PG and PA is correlated with the prediction per imaging modality. In ▶ **Table 2** sensitivity, specificity, PPV and NPV are reported per-lesion for each imaging technique, along with the 95 % Clopper–Pearson confidence intervals.

A sub-analysis was performed to achieve more information about the level of significance. Per-lesion sensitivity and specificity were compared between two imaging techniques at a time with the McNemar test, only using paired data. The output of the significance in difference of the per-lesion sensitivity and per-lesion specificity is reported in ▶ **Table 3**. 4D-CT is not mentioned because no significant difference was found due to limited data.

MET-PET/CT after inconclusive US and/or subtraction scintigraphy

Ten patients underwent a MET-PET/CT after negative or contradictive prior US and/or subtraction scintigraphy. In seven of these patients (70 %) MET-PET/CT predicted the adenomas better than US and/or subtraction scintigraphy. In two patients (20 %) the value of MET-PET/CT was comparable to US and/or subtraction scintigraphy. In one case (10 %) MET-PET/CT was inferior to subtraction scintigraphy.

Ectopic adenomas

Out of the five ectopic adenomas, two could not be detected on imaging. Not every patient underwent every imaging technique: US and subtraction scintigraphy detected one out of five adenomas; MET-PET/CT detected two out of two adenomas. Subtraction scintigraphy two times falsely predicted an ectopic adenoma, because eventually, there was no ectopic adenoma found during sur-

▶ **Table 2** Per-lesion sensitivity, specificity, PPV, and NPV for each imaging modality.

	Sensitivity	Specificity	PPV	NPV
US	36/90 40.0 % [29.8; 50.9]	211/221 95.5 % [91.8; 97.8]	36/46 78.3 %	211/265 79.6 %
Subtraction scintigraphy	24/75 32.0 % [21.7; 43.8]	169/185 91.4 % [86.3; 95.0]	24/40 60.0 %	169/220 76.8 %
MET-PET/CT	13/22 59.1 % [36.4; 79.3]	44/46 95.7 % [85.2; 99.5]	13/15 86.7 %	44/53 83.0 %
4D-CT	5/8 62.5 % [24.5; 91.5]	24/25 96.0 % [79.6; 99.9]	5/6 83.3 %	24/27 88.9 %

US: Ultrasound; MET-PET/CT: [^{11}C]-Methionine positron emission tomography-computed tomography; 4D-CT: 4-Dimensional computed tomography; PPV: Positive predictive value; NPV: Negative predictive value. In square brackets: 95 % Clopper–Pearson confidence intervals (%).

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▶ **Table 3** Significance of difference between two techniques for per-lesion sensitivity/specificity (paired data only).

Per-lesion sensitivity			Per-lesion specificity		
Technique 1	**Technique 2**	**p-value**	**Technique 1**	**Technique 2**	**p-Value**
US *	Subtraction scintigraphy	1.000	US *	Subtraction scintigraphy	0.035 (°)
US	MET-PET/CT *	0.039 (°)	US *	MET-PET/CT	1.000
Subtraction scintigraphy	MET-PET/CT *	0.070	Subtraction scintigraphy	MET-PET/CT *	1.000

US: Ultrasound; MET-PET/CT: [^{11}C]-Methionine positron emission tomography-computed tomography. * The technique with the highest per-lesion sensitivity/specificity. (°) A significant difference in per-lesion sensitivity/specificity between the two techniques. Statistics were performed using the McNemar test.

gery or on pathological analysis. Other imaging modalities never showed false positive ectopic adenomas.

MGD

Only two of the nine patients with MGD (both had four hyperplastic parathyroid glands) underwent MET-PET/CT in whom only one hyperplastic gland per patient was predicted correctly. This produces a per-lesion sensitivity of 25 % for MET-PET/CT in MGD. US and subtraction scintigraphy had a per-lesion sensitivity of respectively 20.8 and 25 % in MGD and was performed in eight and seven patients, respectively. No 4D-CT was performed in patients with MGD. No false positive results are present in this study for MGD.

Preoperative PTH levels

For every imaging modality the pre-operative PTH levels were correlated with the accuracy of prediction of pathological glands. The results are shown in ▶ **Fig. 2** and ▶ **Fig. 3**. Based on these graphs no difference in preoperative PTH is seen for US and subtraction scintigraphy. But for MET-PET/CT and 4D-CT, the preoperative PTH level is markedly higher in true positive cases. Concerning the preoperative calcium levels, no such differences were seen.

Discussion

MET-PET/CT demonstrated a higher sensitivity compared to subtraction scintigraphy and US showed a higher specificity compared to subtraction scintigraphy, based on the results in ▶ **Table 2.** This assumption is made since the means are not or very little incorporated in the confidence intervals. It is important to note that the sensitivity of MET-PET/CT is possibly underestimated as it is mainly performed in patients with inconclusive results on US and/or subtraction scintigraphy. Since the resolution of PET (in MET-PET/CT) is higher than in SPECT or planar gamma-camera imaging (in subtraction scintigraphy), this could be part of the explanation for the higher sensitivity of MET-PET/CT. The higher specificity of US compared to subtraction scintigraphy could be explained by the subspecialization of the radiologist in our center, since he is performing many endocrine-related US.

Two techniques were compared at a time using the McNemar test, as demonstrated in ▶ **Table 3**, to calculate levels of significance. This shows significantly better sensitivity of MET-PET/CT compared to US with a p-value of 0.039, respectively, and a similar trend but without reaching significance for per-lesion sensitivity when compared to subtraction scintigraphy with a p-value of 0.070. As for the specificity, US is significantly better than subtraction scintigraphy with a p-value of 0.035.

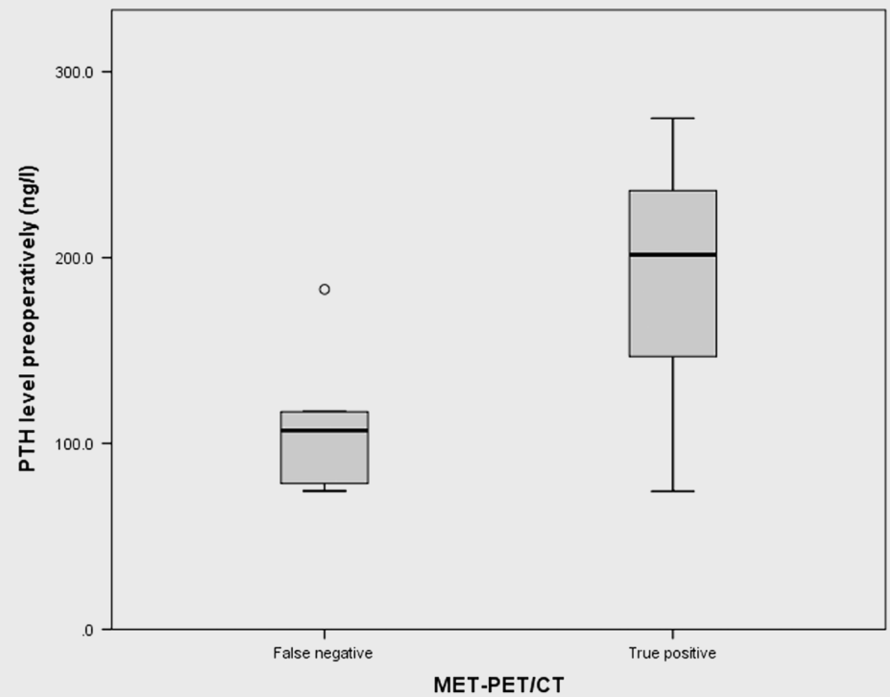
The strength of this retrospective study is the large cohort, consisting of 84 patients, with PHPT, who underwent excisional surgery.

To our knowledge, this is the first study to investigate and report the relationship between the preoperative level of PTH and the prediction by the several imaging modalities, especially MET-PET/CT. It has been determined that a preoperative PTH level above 120 ng/l is linked to a correct prediction by MET-PET/CT in this population of 16 patients. For 4D-CT a cut-off around 200 ng/l was observed. The most obvious explanation is that parathyroid adenomas with higher secretory activity, resulting in higher PTH, are easier to detect with these techniques, since they are based on uptake of respectively [^{11}C]-methionine and iodine contrast. Based on our study, we could cautiously state that MET-PET/CT and 4D-CT are especially useful in patients with high preoperative PTH levels. This could lead to a more focused approach, but for conclusive statements, more studies will be needed.

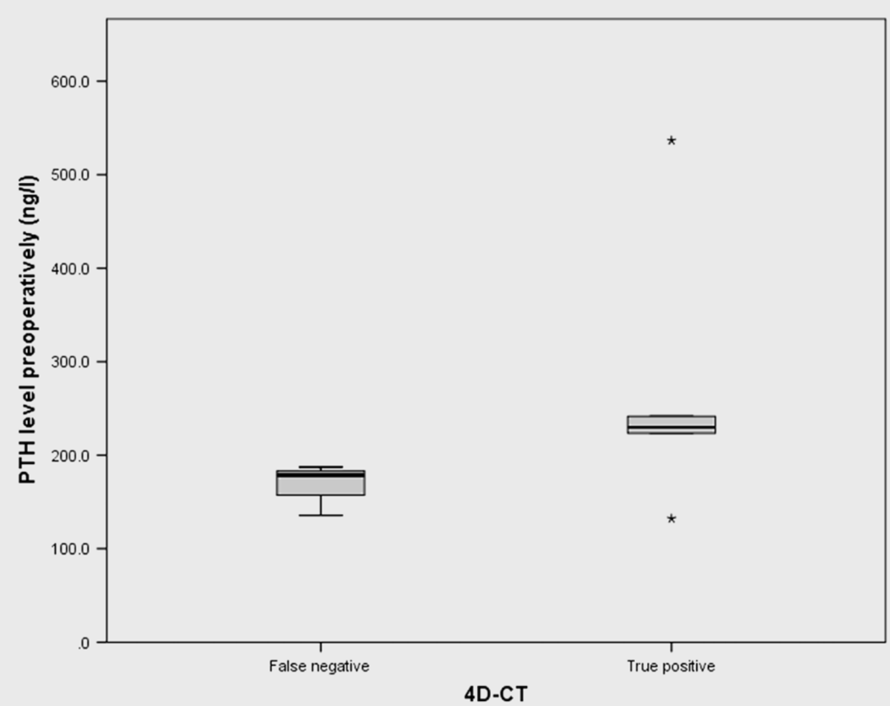
Only patients who underwent surgery for primary hyperparathyroidism were included. Because of strict exclusion criteria, it was possible to focus on the intrinsic value of the imaging techniques without confounding factors. Nevertheless, we need to consider some possible weaknesses in this retrospective study.

First, it is important to note that, in most cases, MET-PET/CT was performed later than US or subtraction scintigraphy. By consequence, the adenomas could have become larger or more active and easier to detect by the time MET-PET/CT was executed. Secondly, it was not possible to track down to what extent the interpretation of imaging results was influenced by previous imaging results.

To maximally exclude these previous shortcomings, further research in a prospective setting is needed. Ideally every patient would undergo every imaging technique within a limited time period, with multiple interpreters per imaging modality and with standardized laboratory tests. Up until then MET-PET/CT will con-



► **Fig. 2** Boxplot of preoperative PTH levels, grouped for prediction by MET-PET/CT (n = 16). MET-PET/CT, [^{11}C]-methionine positron emission tomography-computed tomography. PTH: Parathyroid hormone. ° Outlying data of more than 1.5 times the interquartile range This boxplot compares the preoperative PTH level of patients where MET-PET/CT falsely predicted the parathyroid adenoma and where MET-PET/CT correctly predicted the parathyroid adenoma.



► **Fig. 3** Boxplot of preoperative PTH levels, grouped for prediction by 4D-CT (n = 8). 4D-CT, 4-dimensional computed tomography; PTH, parathyroid hormone. * Outlying data of more than 3 times the interquartile range. This boxplot compares the preoperative PTH level of patients where 4D-CT falsely predicted the parathyroid adenoma and where 4D-CT correctly predicted the parathyroid adenoma.

tinue to be a second line imaging technique. Also the limited availability of the [^{11}C]-methionine tracer, due to its short half-life and the need for a cyclotron nearby, will not facilitate its use in first line. [^{18}F]-Fluorocholine might therefore be an attractive alternative to include in future prospective studies.

Based on this study, no definite conclusions can be made for 4D-CT since only eight patients underwent this technique. There were no conclusions drawn regarding ectopic adenomas since only five cases were identified. Caution in the interpretation of the value of MET-PET/CT in MGD is required since the population is small, though it suits the general finding that MET-PET/CT has a lower value in MGD [25, 43].

The effective radiation dose of subtraction scintigraphy was two times higher than those of MET-PET/CT and 4D-CT. Nevertheless, these radiation burdens are still relatively low. Though this can be kept in mind in the decision making in vulnerable groups, for example, children and pregnant women.

In conclusion, MET-PET/CT seems a valuable imaging modality in primary hyperparathyroidism, at least as second line imaging approach, with higher per-lesion sensitivity than US and subtraction scintigraphy in such setting. US showed a higher per-lesion specificity than subtraction scintigraphy. Especially when US and/or subtraction scintigraphy are inconclusive or negative, MET-PET/CT directs the clinician and surgeon to the correct localization of the adenoma in 70 % of the cases.

Acknowledgements

As this manuscript originated from a master thesis project, I would like to thank my promotor (Prof. B. Bravenboer) for his guidance on this journey, as well as my co-promotor (Prof. M. Keyaerts) for her additional insights.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Garmendia Madariaga A, Santos Palacios S, Guillén-Grima F et al. The incidence and prevalence of thyroid dysfunction in Europe: A meta-analysis. J Clin Endocrinol Metab 2014; 99: 923–931

[2] Fraser WD. Hyperparathyroidism. Lancet 2009; 374: 145–158

[3] Bilezikian JP, Bandeira L, Khan A et al. Hyperparathyroidism. Lancet 2018; 391: 168–178

[4] Bhadada SK, Arya AK, Mukhopadhyay S et al. Primary hyperparathyroidism: insights from the Indian PHPT registry. J Bone Miner Metab 2018; 36: 238–245

[5] Hindie E, Zanotti-Fregonara P, Tabarin A et al. The role of radionuclide imaging in the surgical management of primary hyperparathyroidism. J Nucl Med 2015; 56: 737–744

[6] Udelsman R, Akerstrom G, Biagini C et al. The surgical management of asymptomatic primary hyperparathyroidism: Proceedings of the Fourth International Workshop. J Clin Endocrinol Metab 2014; 99: 3595–3606

[7] Bilezikian JP. Primary hyperparathyroidism. Endocr Pract 2012; 18: 781–790

[8] Agha A, Hornung M, Stroszczynski C et al. Highly efficient localization of pathological glands in primary hyperparathyroidism using contrast-enhanced ultrasonography (CEUS) in comparison with conventional ultrasonography. J Clin Endocrinol Metab 2013; 98: 2019–2025

[9] Bergenfelz AO, Jansson SK, Wallin GK et al. Impact of modern techniques on short-term outcome after surgery for primary hyperparathyroidism: A multicenter study comprising 2,708 patients. Langenbecks Arch Surg 2009; 394: 851–860

[10] Ishibashi M, Nishida H, Hiromatsu Y et al. Comparison of technetium-99m-MIBI, technetium-99m-tetrofosmin, ultrasound and MRI for localization of abnormal parathyroid glands. J Nucl Med 1998; 39: 320–324

[11] Kedarisetty S, Fundakowski C, Ramakrishnan K et al. Clinical Value of Tc99m-MIBI SPECT/CT Versus 4D-CT or US in Management of Patients With Hyperparathyroidism. Ear Nose Throat J 2019; 98: 149–157

[12] Raeymaeckers S, De Brucker Y, Vanderhasselt T et al. Detection of parathyroid adenomas with wide-beam multiphase CT. Towards a true 4-dimensional visualization technique with quantitative analysis of perfusion parameters. Conference; November. 2018; Chicago

[13] Day KM, Elsayed M, Beland MD et al. The utility of 4-dimensional computed tomography for preoperative localization of primary hyperparathyroidism in patients not localized by sestamibi or ultrasonography. Surgery 2015; 157: 534–539

[14] Madorin CA, Owen R, Coakley B et al. Comparison of radiation exposure and cost between dynamic computed tomography and sestamibi scintigraphy for preoperative localization of parathyroid lesions. JAMA Surg 2013; 148: 500–503

[15] Cheung K, Wang TS, Farrokhyar F et al. A meta-analysis of preoperative localization techniques for patients with primary hyperparathyroidism. Ann Surg Oncol 2012; 19: 577–583

[16] Hellman P, Ahlstrom H, Bergstrom M et al. Positron emission tomography with 11C-methionine in hyperparathyroidism. Surgery 1994; 116: 974–981

[17] Sundin A, Johansson C, Hellman P et al. PET and parathyroid L-[carbon-11]methionine accumulation in hyperparathyroidism. J Nucl Med 1996; 37: 1766–1770

[18] Yuan L, Liu J, Kan Y et al. The diagnostic value of 11C-methionine PET in hyperparathyroidism with negative 99mTc-MIBI SPECT: A meta-analysis. Acta Radiol 2017; 58: 558–564

[19] Rubello D, Fanti S, Nanni C et al. 11C-methionine PET/CT in 99mTc-sestamibi-negative hyperparathyroidism in patients with renal failure on chronic haemodialysis. Eur J Nucl Med Mol Imaging 2006; 33: 453–459

[20] Tang BN, Moreno-Reyes R, Blocklet D et al. Accurate pre-operative localization of pathological parathyroid glands using 11C-methionine PET/CT. Contrast Media Mol Imaging 2008; 3: 157–163

[21] Lenschow C, Gassmann P, Wenning C et al. Preoperative (1)(1) C-methionine PET/CT enables focused parathyroidectomy in MIBI-SPECT negative parathyroid adenoma. World J Surg 2015; 39: 1750–1757

[22] Noltes ME, Coester AM, van der Horst-Schrivers ANA et al. Localization of parathyroid adenomas using (11)C-methionine pet after prior inconclusive imaging. Langenbecks Arch Surg 2017; 402: 1109–1117

[23] Chun IK, Cheon GJ, Paeng JC et al. Detection and Characterization of Parathyroid Adenoma/Hyperplasia for Preoperative Localization: Comparison Between (11)C-Methionine PET/CT and (99m)Tc-Sestamibi Scintigraphy. Nucl Med Mol Imaging 2013; 47: 166–172

[24] Weber T, Gottstein M, Schwenzer S et al. Is C-11 Methionine PET/CT Able to Localise Sestamibi-Negative Parathyroid Adenomas? World J Surg 2017; 41: 980–985

[25] Braeuning U, Pfannenberg C, Gallwitz B et al. 11C-methionine PET/CT after inconclusive 99mTc-MIBI-SPECT/CT for localisation of parathyroid adenomas in primary hyperparathyroidism. Nuklearmedizin 2015; 54: 26–30

[26] Caldarella C, Treglia G, Isgro MA et al. Diagnostic performance of positron emission tomography using (1)(1)C-methionine in patients with suspected parathyroid adenoma: a meta-analysis. Endocrine 2013; 43: 78–83

[27] Kluijfhout WP, Pasternak JD, Drake FT et al. Use of PET tracers for parathyroid localization: A systematic review and meta-analysis. Langenbecks Arch Surg 2016; 401: 925–935

[28] Weber T, Cammerer G, Schick C et al. C-11 methionine positron emission tomography/computed tomography localizes parathyroid adenomas in primary hyperparathyroidism. Horm Metab Res 2010; 42: 209–214

[29] Michaud L, Burgess A, Huchet V et al. Is 18F-fluorocholine-positron emission tomography/computerized tomography a new imaging tool for detecting hyperfunctioning parathyroid glands in primary or secondary hyperparathyroidism? J Clin Endocrinol Metab 2014; 99: 4531–4536

[30] Leung K. [(18)F]Fluorocholine.In: Molecular Imaging and Contrast Agent Database (MICAD). Bethesda (MD): National Center for Biotechnology Information (US);2004–2013; Available from: https://www.ncbi.nlm.nih.gov/books/NBK5330/

[31] Lezaic L, Rep S, Sever MJ et al. (1)(8)F-Fluorocholine PET/CT for localization of hyperfunctioning parathyroid tissue in primary hyperparathyroidism: a pilot study. Eur J Nucl Med Mol Imaging 2014; 41: 2083–2089

[32] Michaud L, Balogova S, Burgess A et al. A Pilot Comparison of 18F-fluorocholine PET/CT, Ultrasonography and 123I/99mTc-sestaMIBI Dual-Phase Dual-Isotope Scintigraphy in the Preoperative Localization of Hyperfunctioning Parathyroid Glands in Primary or Secondary Hyperparathyroidism: Influence of Thyroid Anomalies. Medicine (Baltimore) 2015; 94: e1701

[33] Kluijfhout WP, Pasternak JD, Gosnell JE et al. (18)F Fluorocholine PET/MR Imaging in Patients with Primary Hyperparathyroidism and Inconclusive Conventional Imaging: A Prospective Pilot Study. Radiology 2017; 284: 460–467

[34] Beheshti M, Hehenwarter L, Paymani Z et al. (18)F-Fluorocholine PET/CT in the assessment of primary hyperparathyroidism compared with (99m)Tc-MIBI or (99m)Tc-tetrofosmin SPECT/CT: A prospective dual-centre study in 100 patients. Eur J Nucl Med Mol Imaging 2018; 45: 1762–1771

[35] Broos WAM, van der Zant FM, Knol RJJ et al. Choline PET/CT in parathyroid imaging: A systematic review. Nucl Med Commun 2019; 40: 96–105

[36] Treglia G, Piccardo A, Imperiale A et al. Diagnostic performance of choline PET for detection of hyperfunctioning parathyroid glands in hyperparathyroidism: A systematic review and meta-analysis. Eur J Nucl Med Mol Imaging 2019; 46: 751–765

[37] Wilhelm SM, Wang TS, Ruan DT et al. The American Association of Endocrine Surgeons Guidelines for Definitive Management of Primary Hyperparathyroidism. JAMA Surg 2016; 151: 959–968

[38] Payne RB, Little AJ, Williams RB et al. Interpretation of serum calcium in patients with abnormal serum proteins. Br Med J 1973; 4: 643–646

[39] Jassam N, Gopaul S, McShane P et al. Calcium adjustment equations in neonates and children. Ann Clin Biochem 2012; 49: 352–358

[40] Castellano E, Attanasio R, Boriano A et al. Sex Difference in the Clinical Presentation of Primary Hyperparathyroidism: Influence of Menopausal Status. J Clin Endocrinol Metab 2017; 102: 4148–4152

[41] Deloar HM, Fujiwara T, Nakamura T et al. Estimation of internal absorbed dose of L-[methyl-11C]methionine using whole-body positron emission tomography. Eur J Nucl Med 1998; 25: 629–633

[42] Christner JA, Kofler JM, McCollough CH. Estimating effective dose for CT using dose-length product compared with using organ doses: consequences of adopting International Commission on Radiological Protection publication 103 or dual-energy scanning. AJR Am J Roentgenol 2010; 194: 881–889

[43] Hayakawa N, Nakamoto Y, Kurihara K et al. A comparison between 11C-methionine PET/CT and MIBI SPECT/CT for localization of parathyroid adenomas/hyperplasia. Nucl Med Commun 2015; 36: 53–59

