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Use of 6-[¹⁸F]-fluorodopamine positron emission tomography as first-line investigation for the diagnosis and localization of non-metastatic and metastatic pheochromocytoma

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Summary

Objective—Imaging modalities available for the localization of pheochromocytoma (PHEO) include computed tomography (CT), magnetic resonance imaging (MRI), [¹²³I]- or [¹³¹I]-labeled metaiodobenzylguanidine (^{123/131}I-MIBG) scintigraphy and 6-[¹⁸F]-fluorodopamine (¹⁸F-FDA) positron emission tomography (PET). Our aim was to investigate the yield of ¹⁸F-FDA PET versus biochemical testing and other imaging techniques to establish the diagnosis and location of PHEO.

Patients and measurements—The study included 99 consecutive patients (35 M, 64 F, mean $\pm$ SD age 46.4 $\pm$ 13.4 years), who underwent ¹⁸F-FDA PET, biochemical testing (plasma catecholamines and free metanephrines) and CT and/or MRI. The majority (78%) also underwent ^{123/131}I-MIBG.

Results—26 patients had non-metastatic PHEO, 34 patients had metastatic PHEO, and PHEO was ruled out in 39 patients. Investigations to rule out or confirm PHEO yielded the following sensitivity/specificity: plasma metanephrines 97/95%, ¹⁸F-FDA 92/90%, ¹²³I-MIBG 83/100%, ^{123/131}I-MIBG 70/100%, CT 100/41%, MRI 98/60%. Sensitivities for localizing non-metastatic PHEO on a per-lesion base were: CT 97%, MRI 92%, ¹⁸F-FDA 78%, ¹²³I-MIBG 78% and ^{123/131}I-MIBG 76%. Sensitivities for detecting metastases on a per-patient base were: CT and MRI 100%, ¹⁸F-FDA 97%, ¹²³I-MIBG 85%, and ^{123/131}I-MIBG 65%.

Conclusion—For tumor localization, ¹⁸F-FDA PET and ^{123/131}I-MIBG scintigraphy perform equally well in patients with non-metastatic PHEO, but metastases are better detected by ¹⁸F-FDA PET than by ^{123/131}I-MIBG.

Keywords

paraganglioma; positron emission tomography; imaging; fluorodopamine; metanephrines

Introduction

Pheochromocytoma (PHEO) is a chromaffin cell tumor that produces catecholamines. Most PHEOs develop from the adrenal medulla, but they may also derive from sympathetic paraganglia in extra-adrenal abdominal or thoracic locations. 1 Although PHEO is a rare cause of hypertension, the diagnosis is considered frequently by clinicians in patients with refractory hypertension or symptoms or signs of catecholamine excess. Plasma levels of fractionated free metanephrines are considered the gold standard to confirm or rule out the presence of PHEO. 2 Biochemical evidence of PHEO is followed by efforts to localize the tumor. Widely available imaging modalities for localization of PHEO include computed tomography (CT), magnetic resonance imaging (MRI), and [^{123}I] or [^{131}I]-labeled metaiodobenzylguanidine ($^{123/131}\text{I}$ -MIBG) scintigraphy. CT and MRI offer high sensitivity but low specificity for unequivocally identifying PHEO. Distorted anatomy or surgical clips can also compromise results of anatomical imaging. $^{123/131}\text{I}$ -MIBG is a highly specific agent that is transported into neurosecretory granules of catecholamine-producing cells via the vesicular monoamine transporters after uptake into chromaffin cells by the norepinephrine transporter. 3 However, the sensitivity of $^{123/131}\text{I}$ -MIBG is somewhat limited, especially for metastatic PHEO. 4–6 PHEO cells are targeted through a similar mechanism by 6- ^{18}F -fluorodopamine (^{18}F -FDA), a recently developed agent available for positron emission tomography (PET) 7 and also by ^{11}C -hydroxyephedrine and ^{11}C -epinephrine. 8;9 ^{18}F -FDA PET offers excellent sensitivity and specificity for the localization of both non-metastatic and metastatic PHEO. 4;7;10;11 Besides $^{123/131}\text{I}$ -MIBG and ^{18}F -FDA, agents that accumulate in PHEO cells through different mechanisms such as 6- ^{18}F -fluoro-L-3,4-dihydroxyphenylalanine (^{18}F -DOPA) and - ^{18}F -fluoro-2-deoxy-D-glucose (^{18}F -FDG) PET are increasingly recognized as alternatives to localize certain types of PHEO. 4;12–14

In the Europe and the United States and, patients with a high clinical suspicion of PHEO are typically referred to specialized physicians, usually endocrinologists, who practice in a secondary or tertiary health care setting. In such clinical settings, including the National Institutes of Health (NIH), the a priori chance of finding PHEO in referred patients is relatively high. Accurate and swift establishment of the diagnosis and localization of the tumor is critical for directing appropriate treatment. Considering the excellent sensitivity and specificity of ^{18}F -FDA PET, we hypothesized, that performing ^{18}F -FDA PET as first line investigation in such patients would provide a good alternative to biochemical testing to confirm or rule out the presence of PHEO, and to localize the tumor at the same time. We therefore performed a prospective study in a large group of patients with known or suspected PHEO and compared the yield of ^{18}F -FDA PET with biochemical testing, $^{123/131}\text{I}$ -MIBG scintigraphy, and anatomical imaging with respect to establishing the diagnosis and location of PHEO. For non-metastatic PHEO, surgical pathology of the removed tumor served as the “gold standard” diagnostic criterion. Reviews of anatomical and functional scanning results were performed by investigators who were blinded to any associated clinical findings.

Materials and methods

Subjects

The study included 99 patients (35 M, 64 F, mean $\pm$ SD age 46.4 $\pm$ 13.4 years) who were consecutively referred to the National Institutes of Health (NIH) for known or suspected PHEO, and underwent ^{18}F -FDA PET scanning without CT co-localization between August 2001 and February 2005. Most patients were evaluated because of symptoms and signs suggestive of PHEO (n=60), including 10 with a previous history of PHEO and 5 with a (possible) hereditary form of PHEO. Ten asymptomatic patients underwent PHEO screening because of a (possible) hereditary disorder. Others were evaluated for the presence of an

adrenal “incidentaloma” (n=8), or known or suspected metastatic PHEO (n=21). The study protocol was approved by the Institutional Review Board of the National Institutes of Child Health and Development at the NIH. All patients provided written informed consent. All patients underwent biochemical testing, anatomical imaging (CT and/or MRI), and ^{18}F -FDA PET. In addition, most patients underwent ^{123}I -MIBG or ^{131}I -MIBG scintigraphy. Imaging was performed contemporaneously within three months of each other.

Biochemical testing

Plasma was assayed by HPLC for concentrations of free metanephrines and catecholamines, as described previously. All patients were instructed to abstain from caffeine overnight, avoid taking acetaminophen for 5 days before blood sampling, or other medications that could interfere with biochemical tests.

Anatomical imaging

CT from the neck to the pelvis (‘whole body’) was performed with a Hi Speed Advantage Scanner (General Electric Medical Systems, Milwaukee, WI) after rapid infusion of nonionic water-soluble contrast agent as well as oral contrast material. Section thickness was 5–10 mm through the chest and abdomen. MRI was conducted using 1.5 Tesla equipment (General Electric Healthcare Technologies, Waukesha, WI) using phased-array coils for the neck, and either quadrature body or phased-array torso coils for imaging of chest, abdomen, and pelvis, with injection of gadolinium-DTPA unless contraindicated.

^{18}F -FDA PET

PET was performed with a General Electric Advance scanner (General Electric, Milwaukee, WI). Patients were studied after having refrained from caffeine, tobacco, and alcohol for at least 12 hours prior to the scan. ^{18}F -FDA was synthesized as previously described given at specific activity of 7400 to 37000 MBq per millimol. Patients received an activity of 37 MBq intravenously over 3 minutes. Immediately following infusion, 8–15 minute/level emission images were obtained in 2-or 3-dimensional mode from the pelvis to the neck (typically 5–7 levels). At each level, a transmission scan (3–5 minutes) was obtained for attenuation correction.

$^{123}/^{131}\text{I}$ -MIBG scintigraphy

Scintigraphy was initially performed using ^{131}I -labeled MIBG. When ^{123}I -MIBG became available during the course of the study, ^{131}I -MIBG was abandoned and replaced by ^{123}I -MIBG scintigraphy. For whole-body ^{123}I -MIBG and ^{131}I -MIBG scintigraphy, patients were imaged 24 and occasionally 48 h following iv administration of 370 MBq ^{123}I -MIBG or 48 h and occasionally 72 h following 684.5 MBq ^{131}I -MIBG. To protect the thyroid from accumulation of free radioactive iodine, patients took 100 mg of saturated solution of potassium iodide by mouth twice a day for 4 or 8 days with ^{123}I - and ^{131}I -MIBG, respectively, starting the night before ^{123}I - or ^{131}I -MIBG administration. Both planar and single photon emission computed tomography (SPECT) images were obtained with all ^{123}I -MIBG scans.

Data analysis

CT and MRI were read by one radiologist (AL) who was blinded to the biochemical and functional imaging findings. Tumor suspicious lesions were documented in the following locations: adrenal glands, lung, liver, spleen, kidneys, bone, subcutaneous fat and muscle. Region-specific morphological and size criteria for pathologically versus physiologically enlarged lymph nodes were applied as previously suggested. If lesions were identified

as probably benign, such as renal cysts, liver hemangiomas, colon diverticula and gallstones, they were discarded from analysis.

^{18}F -FDA PET and $^{123/131}\text{I}$ -MIBG images were independently reviewed by two nuclear medicine investigators (JAC, CCC) who were blinded to the biochemical and anatomical imaging findings. Areas of non-physiologic uptake were graded using a scale of 1 to 5, where 1 was considered negative for PHEO, 2 was probably negative, 3 equivocal, 4 probably positive and 5 definitely positive. Lesions rated 4 and 5 were considered positive. Any degree of uptake in the region of the adrenal glands on FDA PET scans was considered positive. All differences between the two readers were resolved by consensus review. Since the imaging properties of ^{123}I -MIBG are clearly superior to ^{131}I -MIBG, 23 results of ^{123}I -MIBG and pooled $^{123/131}\text{I}$ -MIBG were analyzed.

Biochemical and imaging results were compared between patients with non-metastatic and metastatic PHEO, and those ultimately shown not to have PHEO. The diagnosis of PHEO required histopathological confirmation. After successful surgical resection of non-metastatic PHEO, patients were discharged from follow-up at the NIH and referred back to their local physician. Metastatic PHEO was defined as histological or radiological evidence of lesions at sites where chromaffin tissue is normally absent. 24 In patients lacking PHEO, the diagnosis was ruled out by a combination of (additional) biochemical investigation, imaging, and clinical follow-up.

To determine the usefulness of plasma free metanephrines versus anatomical and functional imaging as first-line diagnostic tools to confirm or rule out the presence of PHEO, we calculated sensitivity, specificity, and positive and negative predictive values for each modality. In patients with non-metastatic PHEO, the accuracy of different imaging techniques for tumor localization was assessed in reference to lesions that were histopathologically identified as PHEO. Radiologically suspect lesions on anatomical imaging that were also visualized by $^{123/131}\text{I}$ -MIBG scintigraphy and/or ^{18}F -FDA PET were selected for surgical resection. If surgical resection of the culprit lesion(s) resulted in normalization of plasma free metanephrines without signs of recurrence during follow-up, additional lesions on pre-operative imaging were presumed to be false-positive.

In patients with metastatic PHEO, comprehensive histopathological confirmation of all lesions to serve as gold standard for imaging results was not feasible. Therefore, the sensitivity of different imaging modalities in patients with metastatic PHEO was calculated on a per-patient basis only, *i.e.* a technique was scored positive if any lesion(s) were detected in a patient.

Results are given as mean $\pm$ SD unless stated otherwise. The McNemar test was used to compare sensitivity and specificity between different imaging modalities. A two-sided $P<0.05$ was considered significant. Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS for Windows 12; SPSS Inc., Chicago, Illinois, USA).

Results

Diagnosis

Twenty-six patients had non-metastatic PHEO (11 M, 15 F, age 49.1 ± 13.1 y). PHEO locations were left adrenal (N=7), right adrenal (N=12), bilateral adrenal (N=7), and extraadrenal retroperitoneal (N=3). Six of these patients had an underlying mutation of the *RET* proto-oncogene, one of the *succinate dehydrogenase subunit D (SDHD)* gene, one of the *von Hippel-Lindau (VHL)* gene, and one of the *neurofibromatosis type 1 (NF1)* gene. Fourteen patients had sporadic PHEO, and in 3, genetic testing results are pending. Thirty-

four patients had metastatic PHEO (17 M, 17 F, age 43.7 ± 14.4 y) with the following genetic testing results: *succinate dehydrogenase subunit B (SDHB)* (N=13), *RET* (N=2), *VHL* (N=1), sporadic (N=17), results pending (N=1). PHEO was ruled out in 39 patients (6 M, 33 F, age 46.9 ± 12.7 y), including one with a *VHL* mutation and 3 with a *RET* mutation (1 proven, 2 clinically inferred).

Confirming or ruling out PHEO

Plasma metanephrines were determined in all patients. FDA was performed in all patients, and CT, MRI, and either $^{123/131}\text{I}$ -MIBG was performed in most. The numbers of scans performed in the different patient categories are given in Table 1. Plasma metanephrines were elevated in all 26 patients with non-metastatic PHEO, and 32 of 34 with metastatic PHEO. The two patients with normal plasma metanephrines had extensive metastatic disease originating from extra-adrenal tumors and were carriers of an *SDHB* mutation: one of them had an elevated plasma dopamine level of 600 pg/mL (URL 36 pg/mL), whereas in the other (m33), plasma catecholamines and their O-methylated metabolites were consistently normal.

Overall, plasma metanephrines provided a sensitivity of 97% (58/60) and a specificity of 95% (37/39) (Table 2). Plasma metanephrines were compared with imaging studies as first-line investigations to rule out or confirm PHEO (Table 2). Imaging yielded the following per-patient sensitivities and specificities, respectively: ^{18}F -FDA 92% (55/60) and 90% (35/39), ^{123}I -MIBG 83% (34/41) and 100% (22/22), ^{123}I -or ^{131}I -MIBG 70% (38/54) and 100% (24/24), CT 100% (58/58) and 41% (12/29), MRI 98% (50/51) and 60% (15/25). The three false-positive foci on ^{18}F -FDA PET were located in the adrenal regions (2 right, 1 left) and probably represented physiological uptake. $^{123/131}\text{I}$ -MIBG scintigraphy did not show any false-positive lesions.

Localizing non-metastatic PHEO

The sensitivity and specificity of imaging techniques in non-metastatic PHEO are given in Table 3. In 26 patients, a total of 45 foci were detected by anatomical and functional imaging, 32 of which were histologically confirmed PHEOs and 13 were false positives. CT and MRI provided high sensitivity of 97% (31/32) and 92% (24/26), respectively. Sensitivity was similar between ^{18}F -FDA (78%, 25/32), ^{123}I -MIBG (78%, 21/27) and ^{123}I -or ^{131}I -MIBG (76%, 22/29). One right adrenal PHEO was missed by CT and two left adrenal PHEOs by MRI. ^{18}F -FDA failed to detect 7 PHEOs in 6 patients: 1 right adrenal and 2 left adrenal PHEOs with mild ^{18}F -FDA uptake, 2 right adrenal PHEOs without any ^{18}F -FDA uptake, and 2 right adrenal PHEOs that were masked by tracer accumulation in the biliary system and the rim of a renal cyst, respectively. ^{18}F -FDA-negative PHEOs (range 1.5–5 cm) did not differ in size from ^{18}F -FDA-positive PHEOs. Six of the seven PHEOs (three right and three left adrenal) that were missed by ^{18}F -FDA were also missed by ^{123}I -MIBG (4 without and 1 with mild ^{123}I -MIBG uptake) and ^{131}I -MIBG (1 without ^{123}I -MIBG uptake). One additional left adrenal PHEO was missed by ^{123}I -MIBG but positive on ^{18}F -FDA.

The specificity of CT and MRI was relatively poor (Table 3). CT showed 8 false positive foci in the following locations: periportal (n=1), liver (n=1), cervical (n=1), left adrenal (n=2), retroperitoneal (n=2), cervical (n=1) and bone (n=1). MRI showed five false positive foci: retroperitoneal (n=1), liver (n=1), cervical (n=2), mediastinal (n=1). Two out of 3 false positive foci on ^{18}F -FDA PET were located in the left adrenal bed and probably represented physiological uptake, whereas one appeared to be located in the uterus. ^{123}I -MIBG showed one false positive left adrenal focus, again possibly physiologic.

Because of the large number of false-positive findings on CT and MRI, an additional analysis was performed in patients with non-metastatic PHEO. The aim of this secondary analysis was to simulate the diagnostic strategy depicted in Figure 1. According to this strategy, patients with a biochemically established diagnosis of PHEO would first undergo functional imaging, followed by focused CT scanning limited to the level(s) of lesions on functional imaging. Whole body CT scanning would be restricted to patients with negative findings on functional imaging or focused CT. In patients with positive functional imaging results, CT lesions were included in the analysis only if they were located at a similar level as the lesion(s) on functional imaging. Results were extrapolated to 100 patients. This analysis suggests that such a strategy could reduce the field of CT scanning (and thereby radiation exposure and costs) in most patients, yielding a very high sensitivity and specificity, especially when using ^{18}F -FDA PET (Table 4).

Localizing metastatic PHEO

The sensitivity for the detection of metastatic PHEO was 100% for CT and MRI, 97% (33/34) for ^{18}F -FDA, 85% (17/20) for ^{123}I -MIBG, and 65% (20/31) for ^{123}I -or ^{131}I -MIBG ($P=0.002$ versus ^{18}F -FDA, CT and MRI, Table 2).

Discussion

The usefulness of ^{18}F -FDA PET versus biochemical testing, $^{123}/^{131}\text{I}$ -MIBG scintigraphy, and anatomical imaging to establish the diagnosis of PHEO and to localize the tumor was prospectively studied in a large group of patients with non-metastatic or metastatic PHEO, and in patients in whom PHEO was suspected but ruled out. Both plasma metanephrines and ^{18}F -FDA PET provided high sensitivity and specificity (>90%) to confirm or rule out the diagnosis of PHEO. For tumor localization in patients with non-metastatic PHEO, ^{18}F -FDA PET and $^{123}/^{131}\text{I}$ -MIBG scintigraphy had a similar sensitivity of 78%. For the localization of metastases, however, the sensitivity of ^{18}F -FDA PET was clearly superior to $^{123}/^{131}\text{I}$ -MIBG scintigraphy, *i.e.* 97% versus 65%, respectively.

$^{123}/^{131}\text{I}$ -MIBG is the most widely used tracer in the first-line functional imaging of PHEO. ^{123}I -MIBG is preferred over ^{131}I -MIBG because of its higher sensitivity, lower radiation exposure, and improved imaging quality with SPECT. ^{123}I -MIBG scintigraphy was previously shown to have a high sensitivity of 92–98% for non-metastatic PHEO, 5 whereas a lower sensitivity of 57%–79% was reported for metastatic lesions. 4;5;25 In the present study, the superiority of ^{123}I -over ^{131}I -MIBG scintigraphy was confirmed, as was its relatively poor sensitivity for metastases. In search of a better functional imaging agent for the sympathetic nervous system and PHEO, ^{18}F -FDA was developed at the NIH. In our initial studies on ^{18}F -FDA PET in patients with PHEO, all tumors were visualized in nine patients with non-metastatic PHEO, and the presence of metastases was confirmed in all eight patients with malignant disease. 7 In 16 patients with metastatic PHEO, ^{18}F -FDA PET showed a large number of foci that were negative on ^{131}I -MIBG 10. The current study confirms these initial findings of high sensitivity of ^{18}F -FDA PET for the localization of both primary PHEO and metastatic lesions, and its superiority over $^{123}/^{131}\text{I}$ -MIBG scintigraphy in detecting metastases.

Aside from its valuable role in tumor localization in patients with biochemically established PHEO, we show that ^{18}F -FDA PET can also serve as a first-line study to confirm or rule out the diagnosis in patients with a strong clinical suspicion of PHEO in the context of a specialized referral center. Obviously, replacement of biochemical testing by functional imaging is not feasible or cost-effective as a screening method for all patients with possible secondary hypertension or symptoms of catecholamine excess, particularly in a primary health care setting. However, in selected patients with a high a priori chance of PHEO as in

the present study, such an approach offers immediate establishment of the diagnosis and localization of PHEO. A delay in tumor localization and treatment until after laboratory results become available could be avoided by performing ^{18}F -FDA PET as initial investigation. It also allows focused anatomic imaging, with associated cost saving and decreased radiation dose to patients.

^{18}F -FDA PET currently entails several practical limitations. Relatively few centers have the capacity to synthesize ^{18}F -labeled radiopharmaceuticals, although this is likely to expand now that Medicare covers diagnostic ^{18}F -fluorodeoxyglucose PET. In calculating the relative costs of different approaches for diagnostic localization of PHEO, a center should weigh the size of the patient load and length and labor-intensiveness of the radiopharmaceutical synthesis, versus the shorter scanning duration (60 minutes in a single visit) and resulting higher throughput. Advantages of ^{18}F -FDA PET are high resolution and the ability to acquire quantitative information, which might prove valuable in follow-up studies or assessing response to therapy. Because of the short physical half-life of ^{18}F , absorbed radiation doses are smaller than those for typical ^{123}I -MIBG scanning—37 MBq of ^{18}F -FDA corresponds to an effective dose of 0.10 mSv versus 0.71 mSv for 370 MBq ^{123}I -MIBG. The use of combined PET/CT scanners to further improve tumor localization with ^{18}F -FDA, and facilitates the distinction between PHEO and physiological tracer accumulation in normal adrenal tissue, a source of false-positive results in this study.

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The mainstay in PHEO treatment is surgical resection. Pre-surgical imaging serves three purposes: 1. To specifically diagnose PHEO 2. To detect or rule out metastases, and 3. To determine the tumor's anatomical relationship to surrounding structures. The major drawback of anatomical imaging in this context is lack of specificity. CT and MRI commonly detect coincidental adrenal non-chromaffin tumors, as well as many false-positive lesions outside the adrenal beds. On the other hand, functional imaging offers specificity but not the detailed anatomical information required by the surgeon. Our analysis suggests that the favorable characteristics of anatomical and functional imaging are best combined by performing whole body functional imaging first, followed by focused anatomical imaging, restricted to the body region(s) that are positive on ^{18}F -FDA PET or ^{123}I -MIBG scintigraphy.

^{18}F -FDA is only one of a number of functional PET imaging agents used in PHEO. In this study, we did not investigate ^{18}F -DOPA, ^{18}F -FDG, ^{11}C -hydroxyephedrine or ^{11}C -epinephrine, which also yield promising results. 4:8:12-14:27 Previously, we have shown that for the localization of metastases in patients with *SDHB* mutation, ^{18}F -FDG PET is clearly superior to ^{123}I -MIBG scintigraphy and ^{18}F -FDA PET, 4 an observation that may be explained by loss of the cell membrane norepinephrine transporter or the vesicular monoamine transporter, or alternatively by altered glucose metabolism due to *SDHB*-related mitochondrial dysfunction.

In conclusion, for tumor localization, ^{18}F -FDA PET and $^{123}/^{131}\text{I}$ -MIBG scintigraphy perform equally well in patients with non-metastatic PHEO, but metastases are better detected by ^{18}F -FDA PET than by $^{123}/^{131}\text{I}$ -MIBG. After establishing a biochemical diagnosis of PHEO, ^{18}F -FDA PET is an excellent tool to confirm the diagnosis and localize the tumor(s) at the same time. In patients with a high a priori chance of PHEO. Considering the limited availability of ^{18}F -FDA PET, however, ^{123}I -MIBG scintigraphy is still the best available modality in most centers.

Acknowledgments

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Figure 1.
Imaging flow-chart for patients with a biochemically established diagnosis of PHEO

Table 1

Number of scans performed

	Nr. of patients	CT	MRI	CT and/or MRI	[18F]-FDA	[123I]-MIBG	[131I]-MIBG	[123I] or [131I]-MIBG
Non-metastatic								
PHEO	26	26 (100%)	20 (77%)	26 (100%)	26 (100%)	21 (81%)	2 (8%)	23 (88%)
Metastatic PHEO	34	32 (94%)	31 (91%)	34 (100%)	34 (100%)	21 (62%)	10 (29%)	31 (91%)
PHEO total	60	58 (97%)	51 (85%)	60 (100%)	60 (100%)	42 (70%)	12 (20%)	54 (90%)
No PHEO	39	29 (74%)	25 (64%)	31 (79%)	39 (100%)	21 (54%)	2 (5%)	23 (59%)
Total	99	87 (88%)	76 (77%)	91 (92%)	99 (100%)	63 (64%)	14 (14%)	77 (78%)

Table 2

Plasma metanephrines versus imaging as first-line investigations to confirm or rule out PHEO

	plasma NMN/MN	[18F]-FDA	[123I]-MIBG	[123I] or [131I]-MIBG	whole body CT	whole body MRI
Sensitivity	97% (58/60)	92% (55/60)	83% (34/41)	83% (34/41)	100% (58/58)	98% (50/51)
Specificity	95% (37/39)	90% (35/39)	100% (22/22)	100% (24/24)	41% (12/29)	60% (15/25)
Pos. predictive value	97% (58/60)	93% (55/59)	100% (34/34)	100% (38/38)	77% (58/75)	83% (50/60)
Neg. predictive value	95% (37/39)	88% (35/40)	76% (22/29)	60% (24/40)	100% (12/12)	94% (15/16)

Table 3

Localization of PHEO

	[18F]-FDA	[123I]-MIBG	[123I] or [131I]-MIBG	CT	MRI
<i>Non-metastatic PHEO, per lesion analysis</i>					
Sensitivity	78% (25/32)	78% (21/27)	76% (22/29)	97% (31/32)	92% (24/26)
Specificity	77% (10/13)	92% (12/13)	92% (12/13)	38% (5/13) *	58% (7/12)
<i>Metastatic PHEO, per patient analysis</i>					
Sensitivity	97% (33/34)	85% (17/20)	65% (20/31) #	100% (32/32)	100% (31/31)

* P=0.039 versus [123I], and [123I]/[131I] MIBG

P=0.002 versus [18F]-FDA, whole body CT, and whole body MRI

Table 4

Localization of non-metastatic PHEO

	Results of imaging as performed					Projected results for strategy depicted in Figure 1			
	whole body CT	[18F]-FDA	[123I]-MIBG	[123I] or [131I] MIBG		[18F]-FDA and focused CT	[123I]-MIBG and focused CT	[123I] or [131I] MIBG and focused CT	
Nr. of patients available for analysis	26	23	22	24		26	21	23	
<i>% of patients with:</i>									
true positive lesions only	65%	70%	82%	79%		88%	81%	83%	
true positive and false positive lesions	31%	4%	0%	0%		8%	14%	13%	
true positive and false negative lesions	4%	9%	0%	0%		4%	5%	4%	
false positive lesions only	0%	0%	0%	0%		0%	0%	0%	
false positive and false negative lesions	0%	4%	5%	4%		0%	0%	0%	
no lesions (false negative scan)	0%	13%	14%	17%		0%	0%	0%	
<i>Projected nr. of scans needed for 100 patients:</i>									
whole body CT	100	-	-	-		15	19	22	
focused CT	-	-	-	-		88	81	78	
[18F]-FDA	-	100	-	-		100	-	-	
[123I]-MIBG	-	-	100	-		-	100	-	
[123I] or [131I]-MIBG	-	-	-	100		-	-	100	