Diagnostic performance of $[^{124}\text{I}]\text{m-iodobenzylguanidine}$ PET/CT in patients with pheochromocytoma

Manuel Weber$^{1,2}$, Jochen Schmitz$^{1,2}$, Ines Marie$^{1,2}$, Kim Pabst$^{1,2}$, Lale Umutlu$^{2,3}$, Martin Walz$^4$, Ken Herrmann$^{1,2}$, Christoph Rischpler$^{1,2}$, Frank Weber$^{2,5}$, Walter Jentzen$^{1,2}$, Sarah Theurer$^{2,6}$, Thorsten D. Poeppel$^7$, Nicole Unger$^{2,8*}$, and Wolfgang P. Fendler$^{1,2*}$

$^1$Department of Nuclear Medicine, University Hospital Essen, Germany.

$^2$German Cancer Consortium (DKTK), partner site Essen.

$^3$Department of Diagnostic and Interventional Radiology and Neuroradiology, University Hospital Essen, Germany.

$^4$Department of Surgery and Center of Minimally Invasive Surgery, Evangelische Kliniken Essen-Mitte, Academic Teaching Hospital of the University of Duisburg-Essen, Essen, Germany.

$^5$Department of General, Visceral and Transplantation Surgery, Section of Endocrine Surgery, University of Duisburg-Essen, Hufelandstraße, Essen, Germany.

$^6$Institute of Pathology, University Hospital Essen, University Duisburg-Essen, Essen, Germany.

$^7$Nuklearmedizin, MVZ CDT Strahleninstitut, Turiner Str. 2, 50668 Cologne

$^8$Department of Endocrinology and Metabolism, Division of Laboratory Research, University Hospital Essen, University Duisburg-Essen, Essen, Germany.

* Authors contributed equally

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First and corresponding author:

Manuel Weber, MD

Department of Nuclear Medicine, University Hospital Essen

Hufelandstrasse 55

45147 Essen

Germany

FAX: +49-201-723-5964, Phone: +49-201-723-2032

email: manuel.weber@uk-essen.de
ABSTRACT

**Introduction:** $^{123/131}$I-MIBG scintigraphy has shown a high specificity for imaging pheochromocytoma and paraganglioma however with low sensitivity due to low spatial resolution. $^{124}$I-MIBG PET may overcome this limitation to improve the staging of patients with (suspected) pheochromocytoma.

**Methods:** We analyzed the sensitivity, specificity, positive and negative predictive values (PPV, NPV) of $^{124}$I-MIBG PET in 43 consecutive patients with suspected (recurrence of) pheochromocytoma using histopathological (n=25) and clinical validation (n=18) as standard of truth. Furthermore, we compared $^{124}$I-MIBG PET versus contrast enhanced CT (CE-CT) per-patient and per-lesion detection rate of $^{124}$I-MIBG PET in 13 additional patients with known metastatic malignant pheochromocytoma (MMP).

**Results:** $^{124}$I-MIBG PET/CT was positive in 19/43 (44%) patients with suspected pheochromocytoma. Presence of pheochromocytoma was confirmed in 22/43 (51%). $^{124}$I-MIBG PET/CT sensitivity, specificity, PPV, NPV were 86%, 100%, 100%, 88%, respectively. $^{124}$I-MIBG PET was positive in 11/13 (85%) MMP patients. Combined $^{124}$I-MIBG PET and CE-CT detected 173 lesions, of which 166 (96%) and 118 (68%) were visible on $^{124}$I-MIBG PET and CE-CT, respectively.

**Discussion:** $^{124}$I-MIBG PET detects pheochromocytoma with high accuracy at initial staging and high detection rate at re-staging. Future assessment of $^{124}$I-MIBG PET for treatment guidance including personalized $^{131}$I-MIBG therapy is warranted.

**Keywords:** $^{124}$I-MIBG PET, pheochromocytoma, theranostics
INTRODUCTION

Metaiodobenzylguanidine (MIBG) or iobenguane is an analog of the adrenergic neurotransmitter norepinephrine and shows uptake in sympathetically innervated tissues, such as the heart and the salivary glands and tumors that express norepinephrine transporters (1). Due to the high accumulation and retention in sympathicomedullary tissue ¹²³I/¹³¹I-MIBG scintigraphy has been used for decades in the imaging of pheochromocytoma and paraganglioma as well as many neural crest tumors with reported sensitivities and specificities between 80 and 100 % (2-4). The sensitivity is hampered considerably by low spatial resolution making the assessment of small lesions particularly challenging (5). Due to superior technology and workflows, Positron Emission Tomography (PET) expanded rapidly (6) and is now standard imaging modality for most cancer entities including pre-therapeutic imaging in patients with NET (7) and Prostate Cancer (8,9). In patients with pheochromocytoma and paraganglioma somatostatin receptor-targeted PET (10-12) and ¹⁸F-Flubrobenguane (13) have shown a high specific uptake and a high sensitivity. However, ¹²⁴I-MIBG PET comes with several potential advantages:

The similar biodistribution to ¹²³I-MIBG allows for the translation of current concepts for image interpretation (e.g. SIOPEN, CURIE), protocols, and medications established by use of ¹²³I-MIBG scintigraphy (14,15).

Furthermore, ¹²⁴I-MIBG PET potentially combines the high specificity of MIBG imaging with the high sensitivity (5,16) and better quantification of PET tracers (17-19) and thereby addresses major shortcomings of current gamma emitting compounds.

In addition, the long ¹²⁴I half-life (4.18 days) allows for the assessment of pharmacokinetics by performing imaging and blood tests at multiple time points (18,20-23). Following the theranostic principle, the sister compound ¹³¹I-labelled MIBG is applied for radionuclide therapy. In the light of the recent FDA approval of ¹³¹I-MIBG (24) for the treatment of unresectable, locally advanced, and metastatic pheochromocytoma and paraganglioma, pre-therapeutic ¹²⁴I-MIBG PET can provide valuable information on absorbed doses to the tumor and organs at risk and thereby lay the foundation for personalized dosimetry and activity escalation. The potential of the theranostic pair ¹²⁴I/¹³¹I to improve efficacy and mitigate toxicity has previously been shown in the treatment of patients with differentiated thyroid cancer (20,21,23,25) and in a case report on ¹²⁴I/¹³¹I-MIBG (18).

The aim of this retrospective study was to assess the diagnostic performance of ¹²⁴I-MIBG PET in patients with suspected pheochromocytoma and in patients with metastatic malignant
pheochromocytoma (MMP) before $^{131}$I-MIBG therapy. In this intent we analyzed the optimal imaging time point with regards to tumor uptake, the accuracy in comparison to computed tomography, and the rate of upstaging by use of $^{124}$I-MIBG PET in patients with MMP.

**MATERIALS AND METHODS**

**Study designs and Participants**

We screened our institutional database for patients, who underwent $^{124}$I-MIBG PET/CT between March 2005 and March 2017 for suspected (recurrence of) adrenal pheochromocytoma and sufficient follow-up data for validation. The primary endpoint in these patients was the diagnostic performance, defined as sensitivity, specificity as well as negative and positive predictive value (NPV, PPV). Validation was performed histopathologically and - in cases where histopathology was not available - by an experienced, board-certified endocrinologist (N.U.) based on clinical and laboratory parameters. Secondary endpoints were the diagnostic power of quantitative assessment using peak standardized uptake value (SUV$_{\text{peak}}$) for the differentiation between patients where the suspicion of pheochromocytoma was confirmed vs. those where it was ruled out. A subgroup analysis was performed for patients, in whom criteria for an indeterminate adrenal mass were met (size $>10$ mm and $>10$ Hounsfield Units (HU) on non-contrast CT (NC-CT)).

For a second analysis, we included patients with known metastatic malignant pheochromocytoma (MMP). The primary metric in this cohort was the lesion detection rate of $^{124}$I-MIBG PET using the sum of all detected lesions in conjunction with co-acquired contrast-enhanced computed tomography (CE-CT) as reference standard. The protocol was approved by the Ethics Commission of the University of Essen (University of Duisburg-Essen, Medical faculty; protocol number: 20-9656-BO).

$^{124}$I-MIBG synthesis

$^{124}$I-MIBG was manually prepared by the nucleophilic substitution of non-carrier added $^{124}$I-Iodine to MIBG. The labelling was carried out via copper(I)-assisted isotopic Iodine/Iodine exchange. $^{124}$I-Iodine was purchased from PerkinElmer LAS (Rodgau, Germany) in the form of Sodium Iodide (124I) as 0.02 N NaOH solution. Glacial acetic acid (Merck KGaA, Darmstadt) was used as solvent for all other reactants. Typically 100 MBq – 130 MBq of the $^{124}$I-solution were transferred into a testing tube, 10 µl of a sodium disulphite solution (4mg/ml) were added and the mixture was reduced to dryness using a rotating evaporator. 40 µl of a solution containing 100 µg of m-Iodobenzylguanidine (Sigma-Aldrich, Munich) and 1.5 µl of Cu(I)Cl (0.1M, Merck KGaA, Darmstadt) were added to the residue. The mixture was then heated in the stoppered testing tube at 160°C.
for 10 min. After the subsequent reduction to dryness the raw product was resolved in 80 – 100 µl of hydrochloric acid (0.01 M, aq. Sigma-Aldrich, Munich) and the volume was injected into a high-performance liquid chromatography System (Waters) for purification. The semi-preparative high-performance liquid chromatography was performed isocratically using a LiChroCART 250-4 column (Purospher RP-18, 5µm, Merck) with radioactivity and UV Detection (254 nm), the eluent being an aqueous solution of NaH₂PO₄ (1.38 g/L) and acetonitrile 9:1 (v/v). The product peak (retention time 13 min, activity channel) was collected in a round bottom flask and the volume was reduced to dryness and formulated in 5ml of phosphate-buffered saline (PBS). The volume was collected into a syringe and passed through a 0.22-Mm filter (Millex GV, Millipore) directly into a sterile vial (CisBio), yielding 50-70 of formulated ¹²⁴I-MIBG. Quality control of the product was performed using a high-performance liquid chromatography system identical to the semi-preparative run. Purity was determined between 98 % and 100 %

**Imaging Protocol**

PET/CTs were performed on a Siemens Duo (n=40, 71%), Biograph mCT (n=15, 27%), or mMR Biograph (n=1, 2%) 4 hours (n=26), 1 day (n=53), 2 days (n=33), 4/5 days (n=11) after the administration of a mean (interquartile range) activity of 49.8 (48.3-53.0) MBq ¹²⁴I-MIBG. Emission time was 3:30 minutes per bed position for PET/CT and 08:00 minutes for PET/MRI scans. Attenuation correction was performed with the co-acquired CT/MRI scan.

**Image analysis**

SUVpeak was measured in the 5 lesions displaying the highest tracer uptake for each MMP patient at all imaging time points with the aim to identify the imaging time point with the highest average SUVpeak and tumor-to-background (TBR), with SUVmean liver as reference background.

¹²⁴I-MIBG PET/CTs of all preoperative/recurrent pheochromocytomas acquired at this time point were then read by a blinded central reader and pathological findings categorized by anatomical region (adrenal gland, bones, visceral including distant lymph nodes). Size, SUVpeak and HU of the adrenal masses on the NC-CT were measured. In MMP CE-CT and ¹²⁴I-MIBG PET/CTs were anonymized separately and read by a blinded reader with at least two weeks between reading sessions to avoid recall-bias.

**Statistical analysis**

Accuracy of ¹²⁴I-MIBG PET is reported by descriptive statistics. A separate analysis was performed for NC-CT criteria for an indeterminate adrenal mass (>10 HU and >10 mm) and combined ¹²⁴I-MIBG PET and NC-
CT criteria (\(^{124}\)I-MIBG PET positive or adrenal mass >10 HU \textit{and} >10 mm). The detection rate for patients with MMP was defined as the fraction of \(^{124}\)I-MIBG PET-positive lesions among all lesions, CE-CT and \(^{124}\)I-MIBG PET/CT combined. Statistical analysis was performed using IBM SPSS Statistics, version 26 (IBM Corp., Armonk, N.Y., USA). Mann-Whitney U test was performed to test the statistical significance of SUVpeak between patients with and without pheochromocytoma. A receiver operating characteristic (ROC) curve with area under the curve (AUC) as metric was used to determine the predictive potential of SUVpeak for the diagnosis of pheochromocytoma after the exclusion of one patient, in whom images were acquired 2 days after the administration of \(^{124}\)I-MIBG. Youden’s J statistics was performed to identify the optimal cutoff value for the diagnosis of pheochromocytoma based on SUVpeak for all patients and separately for patients, with an indeterminate adrenal mass.

RESULTS

Patient cohort

56 consecutive patients were eligible. In 43/56 patients \(^{124}\)I-MIBG PET was performed for suspected pheochromocytoma due to elevated catecholamine metabolite level, unclear renal mass, and/or clinical appearance; 4 of these were examined due to suspected recurrence after initial resection. Patient characteristics are given in Table 1. The mean patient age (range) was 51.8 (20-74) years. 25/43 (58%) patients were female, 18/43 (42%) male. 3/43 (7%) patients had multiple endocrine neoplasia type IIA, 1/43 patients (2%) had neurofibromatosis 1. Mean (range) levels for Metanephrine and Normetanephrine were 180.9 (15-1,377) pg/ml and 313.8 (28-2,358) pg/ml, respectively.

In 13/56 patients \(^{124}\)I-MIBG PET/CT was performed for known MMP. Mean patient age was 50.9 (17-80) years. 7/13 (54%) patients were female, 6/13 (46%) patients were male.

An overview of MMP patient characteristics is provided in Table 2.

\(^{124}\)I-MIBG tumor uptake

The mean of SUVpeak across all lesions was 13.0, 13.3, 12.0, 9.2 after 4h, 1d, 2d, and 4d/5d, respectively. TBR at 4h, 1d, 2d, and 4d/5d was 1.4, 6.2, 4.9, and 7.6, respectively. Due to the highest tumor SUVpeak and highest number of available data points 1d after \(^{124}\)I-MIBG injection, this time point was used for the subsequent accuracy analyses. In 3 patients, in whom 1d post-injection \(^{124}\)I-MIBG PET/CT was not performed, 2d images were used instead. Figure 1a+b shows the mean SUVpeak across all measured lesions and mean TBR over time.
**124I-MIBG-PET accuracy for suspected pheochromocytoma**

124I-MIBG PET was positive in 19/43 (44%) patients and negative in 24/43 (56%) patients with suspected pheochromocytoma. In 1/19 patients with positive 124I-MIBG PET a local lymph node metastasis was detected. 25/43 patients had adrenal masses with a density >10 HU on NC-CT, in 22 of these, the respective masses were >10 mm.

The suspicion of pheochromocytoma was confirmed in 22/43 (51%) patients and ruled out in 21/43 (49%) patients by the reference standard. Histopathology was available in all cases with confirmed pheochromocytoma and in 3/21 cases (14%), where the presence of pheochromocytoma was ruled out. Of the 22 patients with pheochromocytoma, 21 (95%) had unilateral involvement and 1 (5%) bilateral involvement. In 18/43 (42%) patients the presence of pheochromocytoma was excluded based on clinical records and repeated assessment of serum and urine catecholamine metabolites.

An overview of the diagnostic performance of 124I-MIBG PET is provided in Table 3. Imaging was positive in 19/22 patients with confirmed pheochromocytoma and negative in 21/21 patients, in whom the presence of pheochromocytoma was ruled out, resulting in a sensitivity and specificity of 86% and 100%, respectively.

In all patients with a positive 124I-MIBG PET, pheochromocytoma was histopathologically confirmed, while 3 patients with a negative 124I-MIBG PET would later be diagnosed with pheochromocytoma leading to a PPV and NPV of 100% and 88%, respectively.

NC-CT was available in 36 patients. Of the 25 patients with adrenal masses with >10 HU, pheochromocytoma was confirmed in 18 and ruled out in 7; of the 11 patients with adrenal masses <10 HU, pheochromocytoma was confirmed in one case and ruled out in 10 cases, leading to sensitivity, specificity, PPV, and NPV of 95%, 59%, 72%, and 91% respectively.

Employing an additional size threshold of 10 mm did not affect sensitivity but improved specificity, PPV, and NPV to 76%, 82%, and 93%.

Combined 124I-MIBG PET and NC-CT criteria improved the sensitivity to 100%, specificity to 76%, NPV to 100% and PPV to 84%.

Pheochromocytomas had a significantly higher SUVpeak than unaffected adrenal glands (11.8 vs. 3.5, p<0.001). The AUC for the SUVpeak-based identification of pheochromocytoma was 0.88, with the optimal cutoff value being 5.4. Subgroup analysis of all patients with adrenal lesions with a higher density than 10 HU showed an AUC of 0.90 (sensitivity: 68%, specificity: 100%) for classification into pheochromocytoma vs. non-pheochromocytoma. Separate subgroup analyses of all patients with an indeterminate adrenal mass (HU >10 and size >10 mm; n=22) showed a SUVpeak of 8.5 vs. 2.9 (p<0.001) resulting in AUC of 0.90 (sensitivity: 72%, specificity: 100%) with an optimal cut-off value of 7.0. Figure 2a+b gives an overview over SUVpeak values of patients in which pheochromocytoma was confirmed vs. those where it was ruled out.
In the population of patients with known MMP lesions with increased focal 124I-MIBG uptake were observed in 11/13 (85%) patients. Combined CE-CT and 124I-MIBG PET detected 173 lesions of which 166 (96%) showed increased 124I-MIBG uptake, while 118 (67%) lesions were detected on standalone CE-CT. This led to upstaging from M1a to M1c disease in 1/13 patient (8%) and migration from oligometastatic disease (>5 tumor sites) (26) in 3/13 (23%) patients.

In 5 of these patients, additional 68Ga-DOTATOC-PET/CT was performed. 68Ga-DOTATOC-positive/124I-MIBG-PET-negative lesions were found in two patients, 68Ga-DOTATOC-negative/124I-MIBG PET-positive-lesions were observed in one patient. In the remainder 68Ga-DOTATOC-PET and 124I-MIBG PET yielded identical results with regards to lesion detection, but tumor-specific uptake was higher in 124I-MIBG PET. Figure 3 shows an exemplary patient with MMP and positive 124I-MIBG PET/CT.

**DISCUSSION**

The present study reports high 124I-MIBG PET accuracy at initial staging and high detection rate at re-staging in the - so far - largest published cohort of patients with (suspected) pheochromocytoma. Image acquisition one day after 124I-MIBG PET demonstrated highest SUVpeak and subsequent analyses were performed at this timepoint.

The reported sensitivity of the present study is comparable to that reported in 123I/131I-MIBG scintigraphy studies while the specificity is close to the higher end of reported values (4,27-30). Sensitivity similar to 123I/131I-MIBG is unexpected, as a spatial resolution of PET imaging when compared to scintigraphy might translate into a higher accuracy. Interestingly, patients with false-negative 124I-MIBG PET did not demonstrate particularly small pheochromocytomas (3.0, 2.2 cm, and 4.0 cm, respectively) when compared to the mean size of all resected pheochromocytomas (3.5 cm) implying that biology and norepinephrine transporter expression rather than spatial resolution are critical for lesion detection.

In line with the published literature, NC-CT based assessment has shown a high sensitivity with only one false-negative finding, however at the expense of a low specificity.

As 124I-MIBG PET enables co-acquisition of CE-CT, NC-CT, or MRI it might improve the diagnostic performance over 123I-MIBG scintigraphy taking advantage of the high specificity of functional imaging and the high sensitivity of morphological imaging. Therefore, complementary information of 124I-MIBG PET be of added value in the workup of unclear adrenal lesions when prior diagnostic is inconclusive and to rule out/confirm metastatic spread before local treatment. In our cohort, visual interpretation of 124I-MIBG was superior to semiquantitative
assessment for the diagnosis of pheochromocytoma. Further studies should assess the potential diagnostic value of $^{124}$I-MIBG kinetics in the diagnostic workup of adrenal lesions suspicious of pheochromocytoma. Due to an increase in tumor to background uptake over time, images acquired at late time-points might aide the differentiation of tumor uptake vs. physiological uptake in equivocal lesions.

$^{124}$I-MIBG PET/CT has also shown a high diagnostic performance in patients with MMP, showing additional lesions compared to standalone CE-CT in 7/13 (54%) patients with TNM upstaging in 1/13 (8%) patient and stage migration from oligometastatic disease (26) to disseminated disease in 3/13 (23%) of patients. The high detection rate may impact patient staging, implementation of local treatment and response assessment of systemic or local treatment. Detection of additional tumor sites might also prevent locoregional therapies in disseminated disease when little benefit is to be expected.

In the light of the 2018 FDA approval of $^{131}$I-MIBG radionuclide therapy for MIBG-positive unresectable, locally advanced/metastatic pheochromocytoma and paraganglioma, $^{124}$I-MIBG PET/CT furthermore carries great potential for radionuclide therapy planning:

The long half-life and/or superior quantification of $^{124}$I-MIBG PET/CT when compared to $^{123/131}$I-MIBG scintigraphy facilitate an improved assessment of uptake intensity and kinetics (18,20,31-34). Pre-therapeutic dosimetry of tumor lesions and organs-at-risk enable personalized dosimetry with the goal of maximizing tumor response, while keeping toxicity levels acceptable. The potential of personalized dosimetry for $^{131}$I therapy has previously been described in the context of differentiated thyroid cancer (25,35,36) but data on pheochromocytoma are scarce (18,34,37). In our cohort 86% of patients with known MMP were MIBG-positive. In two patients with at least one $^{124}$I-MIBG-negative lesion, intense $^{68}$Ga-DOTATOC uptake was observed in all lesions, which underpins the theranostic potential of $^{68}$Ga/$^{177}$Lu/$^{90}$Y labelled somatostatin-analogues (38). Prior small retrospective studies identify radiopeptide as a potential treatment option leading to response rates of up to 50 % and disease control rates of up to 100% (39-42).

Limitations of this study include the retrospective study design and the small sample size, as well as the absence of an adrenal-specific CT protocol and magnetic resonance tomography.

**CONCLUSION**

$^{124}$I-MIBG PET detects pheochromocytoma with high accuracy at initial work-up of adrenal mass and re-staging of metastatic disease. Accuracy was similar to the diagnostic performance previously reported for $^{123/131}$I-MIBG scintigraphy. Future studies on the impact of $^{124}$I-MIBG PET on locoregional treatment, personalized $^{131}$I-MIBG therapy, or head-to-head comparison with $^{123/131}$I-MIBG scintigraphy are warranted.
Conflicts of interest

Manuel Weber reports fees from Boston Scientific (speakers bureau) outside of the submitted work. Jochen Schmitz, Ines Maric, Kim Pabst, Lale Umutlu, Martin Walz, Christoph Rischpler, Frank Weber, Walter Jentzen, Sarah Theurer, Thorsten D. Poeppel, and Nicole Unger have nothing to declare.

Ken Herrmann reports personal fees from Bayer SIRTEX, Adacap, Curium, Endocyte, IPSEN, Siemens Healthineers, GE Healthcare, Amgen, Novartis, and ymabs, personal fees and other from Sofie Biosciences, non-financial support from ABX, grants and personal fees from BTG, outside the submitted work.

Wolfgang P. Fendler reports fees from Calyx (consultant), RadioMedix (image review), Bayer (speakers bureau), and Parexel (image review) outside of the submitted work.

KEY POINTS

QUESTION: How is the diagnostic performance of $^{124}$I-MIBG-PET in patients with known or suspected pheochromocytoma?

PERTINENT FINDINGS: $^{124}$I-MIBG-PET has a higher accuracy than non-contrast CT in suspected pheochromocytoma and detects additional lesions in patients with known metastatic pheochromocytoma.

IMPLICATIONS FOR PATIENT CARE: $^{124}$I-MIBG-PET is a promising imaging technique that can provide additional information to cross-sectional imaging and thereby complement the diagnostic workup in patients with known/suspected pheochromocytoma.
REFERENCES


Figure 1a+b. Simple Error Bar with 95% confidence interval plotting mean SUV_{peak_{tumor}} (a) and SUV_{peak_{tumor}}/SUV_{mean_{liver}} (b) of all measured lesions in the $^{124}$I-MIBG-PET-positive MMP patients (n=11) over time.
Figure 2a+b. Adrenal SUVpeak of all patients (a) and patients with indeterminate adrenal masses (b) in whom pheochromocytoma was confirmed vs. those where it was ruled out.
Exemplary patient with metastatic malignant pheochromocytoma who underwent $^{124}$I-MIBG-PET/CT before planned radionuclide therapy. Following image acquisition 4h (a), 1d (b), 2d (c) and 5d (d) a dosimetry-derived activity of 20 GBq $^{131}$I-MIBG was administered leading to lesion absorbed doses between 110 Gy and 320 Gy and a progression-free survival of 54 months. MIBG = Metaiodobenzylguanidine.
Graphical Abstract
Table 1. Characteristics of patients who underwent $^{124}$I-MIBG-PET for suspected pheochromocytoma. P = plasma; MEN = multiple endocrine neoplasia.

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<th>Mean (range)</th>
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<td>Male</td>
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<td>Female</td>
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<td>CATECHOLAMINE METABOLITES</td>
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<td>Metanephrines (P), pg/ml</td>
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<td>Neurofibromatosis</td>
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Table 2. Characteristics of patients who underwent $^{124}$I-MIBG-PET for known metastatic malignant pheochromocytoma.

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<td>Visceral incl. distant lymph nodes</td>
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Table 3. Diagnostic performance of $^{124}$I-MIBG-PET, NC-CT, and combined $^{124}$I-MIBG-PET and NC-CT in patients. NC-CT = non-contrast computed tomography; Sen = Sensitivity; Spe = Specificity; PPV = positive predictive value; NPV = negative predictive value; Acc = accuracy; HU = Hounsfield Units.

<table>
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<td>Sen</td>
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