Superiority of $[^{68}\text{Ga}]-\text{DOTATATE}$ PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma

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TRANSLATIONAL RELEVANCE

Patients with succinate dehydrogenase subunit B (SDHB) mutation-related pheochromocytoma/paraganglioma (PHEO/PGL) are known to suffer from aggressive tumor behavior that has a very high likelihood of metastasis. This work focuses solely on the performance of $[^{68}\text{Ga}]-\text{DOTA(0)-Tyr(3)-octreotate (}[^{68}\text{Ga}]-\text{DOTATATE})$ PET/CT in patients with metastatic SDHB-related PHEOs/PGLs and demonstrates the superiority of $[^{68}\text{Ga}]-\text{DOTATATE}$ PET/CT in the detection of metastatic lesions in these patients, compared to all other and currently recommended functional imaging modalities. Our results may suggest modifying the functional imaging algorithm for these patients, dependent on the clinical setting, which currently places $[^{18}\text{F}]-\text{fluoro-2-deoxy-D-glucose (}[^{18}\text{F}]-\text{FDG})$ PET/CT as the gold standard. Furthermore, our results indicate that peptide receptor radionuclide therapy or treatment with so-called “cold” somatostatin receptor analogs, long-awaited remedies, could be used as new and promising therapeutic options for patients with metastatic SDHB-related PHEOs/PGLs.
ABSTRACT

Purpose: Patients with succinate dehydrogenase subunit B (SDHB) mutation-related pheochromocytoma/paraganglioma (PHEO/PGL) are at a higher risk for metastatic disease than other hereditary PHEOs/PGLs. Current therapeutic approaches are limited but the best outcomes are based on the early and proper detection of as many lesions as possible. Because PHEOs/PGLs overexpress somatostatin receptor 2 (SSTR2), the goal of our study was to assess the clinical utility of [68Ga]-DOTA(0)-Tyr(3)-octreotate ([68Ga]-DOTATATE) positron emission tomography/computed tomography (PET/CT) and to evaluate its diagnostic utility in comparison to the currently recommended functional imaging modalities [18F]-fluorodopamine ([18F]-FDA), [18F]-fluorodihydroxyphenylalanine ([18F]-FDOPA), [18F]-fluoro-2-deoxy-D-glucose ([18F]-FDG) PET/CT as well as CT/magnetic resonance imaging (MRI).

Experimental Design: [68Ga]-DOTATATE PET/CT was prospectively performed in 17 patients with SDHB-related metastatic PHEOs/PGLs. All patients also underwent [18F]-FDG PET/CT and CT/MRI with 16 of the 17 patients also receiving [18F]-FDOPA and [18F]-FDA PET/CT scans. Detection rates of metastatic lesions were compared between all these functional imaging studies. A composite synthesis of all used functional and anatomical imaging studies served as the imaging comparator.

Results: [68Ga]-DOTATATE PET/CT demonstrated a lesion-based detection rate of 98.6% (95% confidence interval (CI) 96.5% to 99.5%), [18F]-FDG, [18F]-FDOPA, [18F]-FDA PET/CT, and CT/MRI showed detection rates of 85.8% (CI 81.3% to 89.4%) (p<0.01), 61.4% (CI 55.6% to 66.9%) (p<0.01), 51.9% (CI 46.1% to 57.7%) (p<0.01), and 84.8% (CI 80.0% to 88.5%) (p<0.01), respectively.
Conclusions: \[^{68}\text{Ga}\]-DOTATATE PET/CT showed a significantly superior detection rate compared to all other functional and anatomical imaging modalities and may represent the preferred future imaging modality in the evaluation of \textit{SDHB}-related metastatic PHEO/PGL.
INTRODUCTION

Pheochromocytomas/paragangliomas (PHEOs/PGLs) are tumors derived from sympathetic tissue in adrenal or extra-adrenal abdominal locations or from parasympathetic tissue in the thorax or head and neck (1). More than 35% of PHEOs/PGLs are hereditary, including multiple endocrine neoplasia 2 (MEN2), von Hippel-Lindau syndrome (VHL), and neurofibromatosis 1 (NF1). In recent years, gene mutations encoding the 4 subunits of the succinate dehydrogenase (SDH) complex (2, 3), fumarate hydratase (FH) (4), MYC-associated factor X (MAX) (5), and hypoxia-inducible factor 2α (HIF2A) (6) have been evaluated and often found to be associated with the presence of multiple and metastatic PHEOs/PGLs.

More than 40% of metastatic PHEOs/PGLs are related to succinate dehydrogenase subunit B (SDHB) mutation carriers (7), who are at high risk for developing metastatic disease. Some studies show a risk of up to 90% (8), with an only 36% 5-year probability of survival after diagnosis of metastatic disease (7). Proper staging and early detection of metastatic disease and evaluation of the extent of metastatic disease in these high risk patients is crucial and has a major effect on a patient’s prognosis, including choosing the necessary treatment and follow-up (9).

Current treatment options in metastatic PHEOs/PGLs are limited and consist of radionuclide therapy with $[^{131}I]$-metaiodobenzylguanidine (MIBG) and chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) (10, 11). Surgery and external beam radiotherapy are less commonly used options in some patients. However, at least 50% of patients with metastatic PHEOs/PGLs, especially those with SDHB mutations, do not benefit from $[^{131}I]$-MIBG treatment due to a lack of the norepinephrine transporter system, resulting in suboptimal or no $[^{131}I]$-MIBG-uptake (12). The use of CVD is a good alternative, but is reserved for patients...
with rapidly growing tumors or extensive organ tumor burden (especially in the liver) and limited by treatment-related toxicity. Thus, there is great interest and need to find new means of therapeutic options, including radionuclide therapy.

PHEOs/PGLs, similar to other neuroendocrine tumors (NETs), are known to express somatostatin receptors (SSTRs) (13) and new, promising radiolabelled DOTA-peptides for SSTR imaging and SSTR-targeting treatment have been developed.

Compared to $[^{111}\text{In}]$-DTPA-octreotide (Octreoscan), which is used for SSTR scintigraphy, the newly developed DOTA-peptides such as DOTA(0)-Tyr(3)-octreotate (DOTATATE), DOTA(0)-Phe(1)-Tyr(3)-octreotide (DOTATOC), and DOTA(1)-Nal(3)-octreotide (DOTANOC) bind to SSTR expressing tumors much more effectively (14). In particular, DOTATATE has a very high affinity for SSTR2, (14), which is overexpressed in most PHEOs/PGLs (13), and has recently been used for their localization (15). Increased expression of SSTR2A and SSTR3 was recently shown in PHEOs/PGLs with $SDH$ deficiency (16), including $SDHB$ mutations.

DOTA-peptides can either be labeled with the diagnostic positron emission tomography (PET) tracer $[^{68}\text{Ga}]$ or therapeutic $\beta$-emitters like $[^{177}\text{Lu}]$ or $[^{90}\text{Y}]$. On one hand, they can provide sensitive SSTR-imaging, enabling improved anatomic localization using PET/computed tomography (CT) technique (17) compared to SSTR scintigraphy. On the other hand, when bound to therapeutic $\beta$-emitters, they can and are used for peptide receptor radionuclide therapy (PRRT) in SSTR overexpressing tumors, especially gastroenteropancreatic NETs (18). Treatment results in metastatic PHEOs/PGLs are also promising (19).

The present study had two main aims: first, to evaluate $[^{68}\text{Ga}]-\text{DOTATATE PET/CT}$ in patients with metastatic $SDHB$-related PHEOs/PGLs and assess their eligibility for future PRRT.
as a new and needed therapeutic approach; and second, to assess the diagnostic value of [$^{68}$Ga]-DOTATATE PET/CT in comparison to other well-established and currently recommended functional imaging studies in PHEOs/PGLs (20), including [$^{18}$F]-fluorodopamine ([$^{18}$F]-FDA), [$^{18}$F]-fluorodihydroxyphenylalanine ([$^{18}$F]-FDOPA), [$^{18}$F]-fluoro-2-deoxy-D-glucose ([$^{18}$F]-FDG) PET/CT, and in comparison to CT/magnetic resonance imaging (MRI). Because histological proof was not possible in many metastatic lesions, the composite of both anatomical and all functional imaging tests was considered the imaging comparator.

**PATIENTS AND METHODS**

**Patients**

Between January and December 2014, 17 consecutive patients (11 men, 6 women) with $SDHB$ mutation-associated PHEOs/PGLs with a mean age of 40.3±14.0 years were prospectively evaluated at the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) at the National Institutes of Health (NIH). All patients had proven metastatic PHEOs/PGLs based on clinical evaluation, including previously found and surgically removed PHEOs/PGLs, biochemical diagnosis, and anatomical and functional imaging.

The study protocol was approved by the institutional review board of the Eunice Kennedy Shriver NICHD (protocol: 00-CH-0093). All patients provided written informed consent for all clinical, genetic, biochemical, and imaging studies regarding PHEOs/PGLs.

Mean age at diagnosis of primary PHEO/PGL in these patients was 30.2±15.0 years. The average interval between diagnosis of a primary tumor and referral to the NIH was 4.5±3.8 years. All 17 patients previously underwent resection of their primary PHEO/PGL. Individual patient characteristics are summarized in Table 1.

[$^{68}$Ga]-DOTATATE in $SDHB$-related PHEOs/PGLs
**Imaging Techniques**

CT scans of the neck, chest, abdomen, and pelvis were performed using the following devices: Siemens Somatom Definition AS, Siemens Somatom Definition Flash, Siemens Medical Solutions; Toshiba Aquilion ONE, Toshiba Medical Systems. Section thickness was up to 3 millimeters (mm) in the neck and 5 mm through the chest, abdomen, and pelvis. All studies were performed with intravenous (i.v.) rapid infusion of nonionic water-soluble contrast agent as well as oral contrast material.

MR scans of the neck, chest, abdomen, and pelvis were obtained with 1.5 and 3 Tesla scanners (Philips Achieva 1.5 and 3 Tesla, Philips Medical Systems; Siemens Verio 1.5 Tesla, Siemens Medical Solutions). Image thickness was 5 mm for all neck studies and 6 mm for chest, abdominal, and pelvic scans. Pre- and post-injection images were obtained in the axial plane. All MR scans included axial T2 series with and without fat saturation, STIR series, and T1 pre- and post-contrast series. MR scans of the abdomen and pelvis also included axial T1 in and out of phase and dynamic THRIVE during infusion of contrast, followed by delayed axial and coronal post-contrast scans after i.v. injection of a gadolinium-diethylenetriamine pentaacetic acid contrast agent.

All 17 patients underwent $^{68}$Ga-DOTATATE, $^{18}$F-FDG PET/CT scanning, and CT/MRI, with 16 also receiving $^{18}$F-FDOPA and $^{18}$F-FDA PET/CT scans.

PET/CT scans from the upper thighs to the skull were performed 60 min after i.v. injection of a mean administered activity of 201.8±39.6 MBq $^{68}$Ga-DOTATATE, 60 min after 362.8±112 MBq $^{18}$F-FDG, 30 min after 458.5±83.1 MBq $^{18}$F-FDOPA, and approximately 8 min after 37.2±1.1 MBq $^{18}$F-FDA. 60 min before each $^{18}$F-FDOPA scan, 200 milligrams (mg)
of carbidopa were administered orally. All PET/CT scans were performed on a Siemens Biograph-mCT 128 PET/CT scanner (Siemens Medical Solutions). PET imaging was obtained in 3D mode. PET images were reconstructed on a 256 x 256 matrix using an iterative algorithm provided by the manufacturer, which also uses time of flight (TOF). Low-dose CT studies for attenuation correction and anatomic co-registration were performed without contrast and used for anatomical localization only.

**Analysis of Data**

$[^{68}\text{Ga}]-\text{DOTATATE}$ PET/CT studies were each read independently by two nuclear medicine physicians blinded to all imaging and clinical data except for the diagnosis, sex, and age of the patient.

Maximal standardized uptake values ($\text{SUV}_{\text{max}}$) were determined and focal areas of abnormal uptake showing a higher $\text{SUV}_{\text{max}}$ than surrounding tissue were considered as lesions. Discrepancies, which occurred in 6 lesions with a mean SUV of 6.2±5.6 in 4 patients, were solved by consensus review. In all other imaging studies, physicians were blinded to $[^{68}\text{Ga}]-\text{DOTATATE}$ PET/CT scans and clinical data except for diagnosis, sex, age of the patient, and previous imaging studies. All imaging studies were performed within 22±15 days of each other. For regional analysis, adrenal glands, liver, abdominal/pelvic compartments (excluding adrenal glands and liver), lungs, mediastinum, and bone were analyzed separately. A patient or region was considered positive regardless of the number of positive findings. Patient-to-patient, region-to-region, and lesion-to-lesion analyses were performed. If the number of lesions in a region exceeded 15, the count was truncated at 15. Patient-, region-, and lesion-related detection rates were compared. Head and neck PGLs were excluded from the analysis in patients with head and
neck PGLs and sympathetic PGLs.

Histologic proof of metastatic lesions was not feasible. The composite of anatomic and all performed functional imaging tests was considered the imaging comparator. A positive result on at least two different functional imaging modalities or at least one functional imaging study and CT/MRI was counted as true disease, whereas a lesion detected only on CT/MRI or only on one functional imaging test while negative on all other used imaging tests was considered a false-positive imaging result.

Statistics

Results are given as means with 95% confidence intervals (CIs) unless stated otherwise. For statistical analysis, the McNemar test was used to compare sensitivities between $[^{68}\text{Ga}]$-DOTATATE PET/CT and the other imaging modalities. A two-sided $p<0.05$ was considered significant.

RESULTS

$[^{68}\text{Ga}]$-DOTATATE PET/CT had a lesion-based detection rate of 98.6% (CI 96.5% to 99.5%), identifying 285 of 289 lesions (mean SUV 56.0±62.1) compared to our defined imaging comparator. Significantly more lesions were identified on $[^{68}\text{Ga}]$-DOTATATE PET/CT compared to all other used functional imaging modalities and CT/MRI (two-sided $p<0.01$ for each imaging modality compared to $[^{68}\text{Ga}]$-DOTATATE PET/CT; corresponding cross tables in Supplemental Figure 1). Lesion-based findings on $[^{68}\text{Ga}]$-DOTATATE PET/CT compared to all other used functional imaging modalities and CT/MRI are summarized and outlined in Tables 2 and 3 as well as in Figure 1. Metastatic lesions were found in the mediastinum, lungs, liver,
abdomen/pelvis, and bones. Those in the mediastinum, abdomen, or pelvis were located in lymphatic nodes. Three bone lesions, which were positive on \([^{18}F]-FDA\) and \([^{18}F]-FDG\) PET/CT, and one lung lesion, which was positive on \([^{18}F]-FDG\) PET/CT and anatomical imaging, were not identified by \([^{68}Ga]-DOTATATE\) PET/CT. A lesion-based evaluation excluding the patient who only received \([^{68}Ga]-DOTATATE\), \([^{18}F]-FDG\) PET/CT, and CT/MRI did not lead to any statistical change.

Besides the 285 lesions confirmed by the defined imaging comparator, \([^{68}Ga]-DOTATATE\) PET/CT detected 33 additional lesions: 8 in mediastinal lymphatic nodes, 10 in retroperitoneal and pelvic lymphatic nodes, and 15 bone lesions (mean SUV 8.2±6.4). All lesions were in the field of view of CT/MR. In the anatomical imaging studies CT/MRI, 8 lesions were reported, which were not positive on any functional imaging study. Two were retroperitoneal lymphatic nodes (1.5 centimeter (cm) and 1.6 cm), 4 were in the lungs (0.4 cm-0.8 cm), and two in the liver (0.7 cm and 0.8 cm). Three mediastinal lesions were only positive in \([^{18}F]-FDG\) PET/CT. Not a single lesion was only positive in either \([^{18}F]-FDOPA\) or \([^{18}F]-FDA\) PET/CT but not another functional or anatomic imaging test.

Per patient detection rates of \([^{68}Ga]-DOTATATE\), \([^{18}F]-FDG\), \([^{18}F]-FDOPA\), \([^{18}F]-FDA\) PET/CT and CT/MRI were 100% (17 out of 17 patients (17/17)), CI 81.6% to 100%, 100% (17/17), CI 81.6% to 100%, 87.5% (14/16), CI 64.0% to 96.5%, 81.3% (13/16), CI 57.0% to 93.4% and 100 % (17/17), CI 81.6% to 100%, respectively.

The per region detection rate for \([^{68}Ga]-DOTATATE\) was 100%, identifying 42 out of 42 regions (42/42), CI 91.6% to 100%, 97.6% for \([^{18}F]-FDG\) (41/42), CI 87.7% to 99.6%, 65.9% for \([^{18}F]-FDOPA\) (27/41), CI 50.6% to 78.4%, 58.4% for \([^{18}F]-FDA\) PET/CT (24/41), CI 43.4% to 72.2%, and 95.2% for CT/MRI (40/42), CI 84.2% to 98.7%.
A PET-imaging example comparing \[^{68}\text{Ga}]-\text{DOTATATE}, \[^{18}\text{F}]-\text{FDG}, \[^{18}\text{F}]-\text{FDOPA}, \text{and} [^{18}\text{F}]-\text{FDA PET/CT} \text{ is shown in Figure 2.}

\textbf{DISCUSSION}

In this study, we evaluated \[^{68}\text{Ga}]-\text{DOTATATE PET/CT} \text{ in a cohort of patients with} \text{SDHB-related} \text{ metastatic PHEOs/PGLs in comparison to} \[^{18}\text{F}]-\text{FDA}, \[^{18}\text{F}]-\text{FDOPA}, \[^{18}\text{F}]-\text{FDG PET/CT}, \text{and CT/MRI. The composite of both anatomical and all functional imaging tests was considered the imaging comparator.} [^{68}\text{Ga}]-\text{DOTATATE PET/CT} \text{ demonstrated a lesion-based detection rate of 98.6\% (CI 96.5\% to 99.5\%), which was significantly superior to all other imaging modalities in this study, thus demonstrating the utility of this modality in localizing tumors in SDHB-related PHEO/PGL. We feel this modality will also be useful in determining the possible eligibility for PRRT in patients with SDHB-related PHEO/PGL.}

Functional imaging agents are able to target PHEOs/PGLs through different mechanisms. \[^{18}\text{F}]-\text{FDA as well as} [^{123}\text{I}]-\text{MIBG specifically target catecholamine synthesis, storage, and secretion pathways, and both enter the cell via the norepinephrine transporter (21, 22). In this study,} [^{18}\text{F}]-\text{FDA had a low lesion-based detection rate of 51.9\% (CI 46.1\% to 57.7\%), which might be explained by tumor dedifferentiation associated with loss of the norepinephrine transporter in these patients. This is supported by the reported} [^{123}\text{I}]-\text{MIBG negativity of more than 50\% of patients in SDHB mutation-associated PHEOs/PGLs (12). Six of the patients in our study had undergone} [^{123}\text{I}]-\text{MIBG-scintigraphy with a very low lesion detection rate of 18.7\% (CI 12.0\% to 27.9\%), but this result was most likely biased by the small patient cohort and the heavy disease burden of our patient population.}
[18F]-FDOPA targets cells via the amino acid transporter system (23) and has demonstrated excellent results in patients with SDHx mutation-related head and neck PGLs (24). However, the lesion-based sensitivity of [18F]-FDOPA in SDHB-related PHEOs/PGLs outside the head and neck regions has been shown to be poor in a previous study (25). The detection rate in our study reached 61.4% (CI 55.6% to 66.9%).

[18F]-FDG is a sensitive but non-specific radiopharmaceutical that enters the cell via glucose transporters (GLUT) (26). Its accumulation is related to increased glucose metabolism as seen in many different types of tumors (26). In SDHB-related metastatic PGLs, its high sensitivity has been well documented (27-29). Higher standardized uptake values (SUV) compared to sporadic and other hereditary PHEO/PGL are also reported, accompanied by an upregulation of hexokinases 2 and 3 (30). Further, it is known that a mutation in the succinate dehydrogenase complex II subunit B can lead to a downregulation or loss of succinate dehydrogenase enzyme activity in the Krebs cycle, resulting in an upregulation of hypoxic angiogenetic pathways via HIFs (6), which force tumor cells to shift from oxidative phosphorylation to aerobic glycolysis (Warburg effect) (31). Currently, [18F]-FDG PET/CT is recommended as the functional imaging technique of choice for patients with metastatic PHEOs/PGLs, including their follow-up and assessment of treatment-related responses (20, 32). In this study, we found a lesion-based detection rate of 85.8% (CI 81.3% to 89.4%) for [18F]-FDG PET/CT.

With a lesion-based detection rate of 98.6% (CI 96.5% to 99.5%), [68Ga]-DOTATATE PET/CT was significantly superior to all other functional imaging modalities in this study. [68Ga]-DOTATATE, which is known to have an approximately 10-fold higher affinity for SSTR2 than [68Ga]-DOTATOC (which also has high affinity to SSTR5) and an approximately
100-fold higher affinity for SSTR2 than $^{[111}\text{In}]$-DTPA-octreotide (14), has already shown excellent results in the imaging of SSTR2 expressing gastroenteropancreatic NETs (33), and PHEOs/PGLs are also known to overexpress predominantly SSTR2 (13). A recent study also demonstrated an increased expression of SSTR2A and SSTR3 in PHEOs/PGLs with SDH deficiency (16), which also supports the approach of SSTR imaging and treatment in these tumors. Until now, there have only been a few small and heterogeneous studies and case reports on imaging of PHEOs/PGLs with DOTA-analogues. These have shown high sensitivities of $^{[68}\text{Ga}]$-DOTATATE and $^{[68}\text{Ga}]$-DOTATOC PET/CT, approaching or reaching 100% (17, 34).

Besides its diagnostic value, $^{[68}\text{Ga}]$-DOTATATE PET/CT can be used to determine which patients may benefit from PRRT, which would be a desirable new treatment option for these patients (7, 8). While PRRT has not been specifically evaluated in $SDHB$-related PHEOs/PGLs yet, it has already been shown to lead to longer progression-free survival, mainly in gastroenteropancreatic NETs (18) but also in other metastatic NETs, including PHEOs/PGLs (35). Unfortunately, PRRT is not approved by the United States Food and Drug Administration at present. In the meanwhile, the high sensitivity of $^{[68}\text{Ga}]$-DOTATATE PET/CT in $SDHB$-related metastatic PHEO/PGL suggests that these patients can be treated with cold SSTR analogs, including sandostatin LAR, lanreotide, or others. Although this approach has not yet been evaluated in PHEOs/PGLs, results using lanreotide in gastroenteropancreatic NETs (36) and individual reports of octreotide treatment in patients with head and neck PGLs support this approach (37, 38). This could also be extremely useful for patients in whom the location or extension of a PHEO/PGL lesion(s) (especially skull base) cannot be accessed by any surgical approach.

The phenomenon of additional lesions appearing with $^{[68}\text{Ga}]$-DOTA-analogues PET/CT
that were not seen by other imaging studies has been reported before (15, 17). Since histologic proof of these lesions in our study was not possible, these lesions have to be discussed as false positive lesions. On the other hand, there are also studies that have reported histological confirmation of SSTR-positive tumor tissue in such cases, which led to a treatment change in up to 60% of patients (39).

Last, the high detection rate of $[^{68}\text{Ga}]-\text{DOTATATE}$ PET/CT in these patients also suggests that the high malignant potential and presumed dedifferentiation of metastatic PHEOs/PGLs in $SDHB$ mutations apparently do not lead to a significant loss of SSTR expression. This is supported by the increased SSTR2A and SSTR3 expression, which was found in $SDH$-deficient tumors (16). Recently, SSTR expression with positive $[^{68}\text{Ga}]-\text{DOTATOC}$ PET/CT was also shown in patients with undifferentiated Epstein-Barr virus-related nasopharyngeal cancer (40). This also indicates that a loss in tumor differentiation is not necessarily combined with a loss in SSTR expression.

In the current guidelines, which do not yet take PET imaging with $[^{68}\text{Ga}]-\text{D}\text{OTA-}\text{peptides}$ into consideration, $[^{18}\text{F}]$-FDG is recommended as first-line functional imaging of $SDHB$-related PHEO/PGL (20). However, our results indicate that $[^{68}\text{Ga}]-\text{DOTATATE}$ PET/CT may have an incremental diagnostic value in the detection of disease sites, which could have an impact on patient care. Therefore, we believe that future guidelines may modify the recommendations in favor of using $[^{68}\text{Ga}]-\text{DOTA-}\text{peptides}$, especially if confirming results from a larger number of patients, sporadic PHEO/PGL patients, and other PHEO/PGL genotypes are made available.

In clinical settings such as the evaluation of treatment response after systemic radionuclide therapy or chemotherapy, the use of $[^{68}\text{Ga}]-\text{DOTATATE}$ PET/CT is still unclear and has to be evaluated. In clinical settings of doubtful CT/MRI results, $[^{68}\text{Ga}]-\text{DOTATATE}$
might also be helpful, although potential false positive results could occur. The more specific functional imaging studies like \(^{[18]F}\)-FDOPA and \(^{[18]F}\)-FDA PET/CT seem to harbor a higher risk for false negative results. Last, \(^{[18]F}\)-FDOPA PET/CT and especially \(^{[18]F}\)-FDA PET/CT are of limited availability, whereas for \(^{[68}Ga\)-DOTATATE PET/CT, we believe broader clinical availability can be expected in the future.

Our study was subject to certain limitations, including the relatively small number of patients and possible bias related to our chosen reference test. Based on this imaging comparator, combined positive findings in functional and/or anatomical imaging studies on one hand cannot fully exclude false positive results (e.g., possible positive lesions in \(^{[68}Ga\)-DOTATATE PET/CT, \(^{[18]F}\)-FDG-PET/CT, and/or CT/MRI related to inflammation or possible positive lesions in \(^{[68}Ga\)-DOTATATE PET/CT, \(^{[18]F}\)-FDOPA PET/CT, and/or CT/MRI related to different neuroendocrine tumors). On the other hand, true positive findings, which only appear in one imaging modality, e.g. CT/MRI, would have been counted as false positive in our setting.

In conclusion, although \(^{[18]F}\)-FDG PET/CT is currently recommended as the functional imaging technique of choice in SDHB-related PHEOs/PGLs and our study is subject to certain limitations, we believe that our results may indicate a preference for \(^{[68}Ga\)-DOTATATE PET/CT in these patients, particularly in the detection of progressive metastatic disease, additional disease sites, and even early detection of metastatic disease. \(^{[68}Ga\)-DOTATATE PET/CT can also be used to help determine the eligibility of patients for PRRT, a new and hopefully soon to be available treatment option. The utility of \(^{[68}Ga\)-DOTATATE PET/CT in other genotypes, sporadic PHEO/PGL, or for treatment monitoring should be evaluated soon.

\(^{[68}Ga\)-DOTATATE in SDHB-related PHEOs/PGLs
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REFERENCES


### Table 1: Individual patient characteristics.

<table>
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<tr>
<th>Pt. #</th>
<th>Sex</th>
<th>SDHB mutation</th>
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<th>Age (s)</th>
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<td>None</td>
<td>0</td>
<td>B, Lu, Me</td>
<td>Res primary</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>c.418G&gt;T, p.Val140Phe</td>
<td>10</td>
<td>20</td>
<td>Aortic bifurcation</td>
<td>NE, NMN, DA</td>
<td>0</td>
<td>B, A/P</td>
<td>Res primary</td>
</tr>
<tr>
<td>4</td>
<td>m</td>
<td>c.689G&gt;A, p.Arg230His</td>
<td>52</td>
<td>52</td>
<td>R para-adrenal</td>
<td>NE, NMN</td>
<td>0</td>
<td>B</td>
<td>RT skull</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>c.343C&gt;T, p.Arg115X</td>
<td>32</td>
<td>43</td>
<td>Urinary bladder</td>
<td>NE, NMN</td>
<td>3</td>
<td>B, Lu, A/P</td>
<td>Res primary, CVD</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>c.689G&gt;A, p.Arg230His</td>
<td>28</td>
<td>50</td>
<td>L carotid body</td>
<td>None</td>
<td>20</td>
<td>Lu, Li</td>
<td>Res primary, CVD</td>
</tr>
<tr>
<td>7</td>
<td>f</td>
<td>c.136C&gt;T, p.Arg46X</td>
<td>19</td>
<td>24</td>
<td>R glomus jugulare</td>
<td>None</td>
<td>0</td>
<td>B, Ne</td>
<td>Res primary, RT skull</td>
</tr>
<tr>
<td>8</td>
<td>m</td>
<td>c.200+33G&gt;A, p.Glu228Glyfsx27</td>
<td>47</td>
<td>59</td>
<td>L para-adrenal</td>
<td>DA, MTT</td>
<td>3</td>
<td>Me, Ne, A/P</td>
<td>Res primary</td>
</tr>
<tr>
<td>9</td>
<td>m</td>
<td>c.136C&gt;T, p.Arg46X</td>
<td>45</td>
<td>46</td>
<td>Urinary bladder</td>
<td>NE, NMN</td>
<td>0</td>
<td>Lu, B</td>
<td>Res primary</td>
</tr>
<tr>
<td>10</td>
<td>m</td>
<td>c.136C&gt;T, p.Arg46X</td>
<td>25</td>
<td>37</td>
<td>R mediastinal</td>
<td>None</td>
<td>0</td>
<td>Lu</td>
<td>Res primary, CVD</td>
</tr>
<tr>
<td>11</td>
<td>m</td>
<td>c.72+1G&gt;T</td>
<td>54</td>
<td>60</td>
<td>R para-adrenal</td>
<td>NE, NMN</td>
<td>0</td>
<td>Lu, Me, A/P, B</td>
<td>Res primary, MIBG</td>
</tr>
<tr>
<td>12</td>
<td>f</td>
<td>Exon 1 deletion</td>
<td>49</td>
<td>55</td>
<td>Aortic bifurcation</td>
<td>NE, NMN, DA, MTT</td>
<td>0</td>
<td>Ne, Me, A/P</td>
<td>Res primary, MIBG</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>c.330_331del, p.Leu111SerfsX7</td>
<td>10</td>
<td>23</td>
<td>L adrenal</td>
<td>NE, NMN</td>
<td>0</td>
<td>B, Lu, Ne, A/P, Li</td>
<td>Res primary</td>
</tr>
<tr>
<td>14</td>
<td>m</td>
<td>c.268C&gt;T, p.Arg90X</td>
<td>11</td>
<td>26</td>
<td>R adrenal</td>
<td>None</td>
<td>8</td>
<td>B, Lu, Ne</td>
<td>Res primary, MIBG</td>
</tr>
<tr>
<td>15</td>
<td>m</td>
<td>Exon 1 deletion</td>
<td>34</td>
<td>41</td>
<td>R para-adrenal</td>
<td>NMN, DA, MTT</td>
<td>5</td>
<td>Me, B</td>
<td>Res primary</td>
</tr>
<tr>
<td>16</td>
<td>m</td>
<td>c.137G&gt;A, p.Arg46Gln</td>
<td>19</td>
<td>36</td>
<td>L pelvis</td>
<td>NE, NMN, DA, MTT</td>
<td>13</td>
<td>B, Lu, Ne, A/P</td>
<td>Res primary, MIBG, CVD</td>
</tr>
<tr>
<td>17</td>
<td>f</td>
<td>c.541-2A&gt;G, splice site mutation</td>
<td>36</td>
<td>54</td>
<td>L carotid body</td>
<td>NE, NMN, DA, MTT</td>
<td>8</td>
<td>B</td>
<td>Res primary</td>
</tr>
</tbody>
</table>
Abbreviations: Age (d), age at diagnosis; age (s), age at study; A/P, abdomen/pelvis; B, bones; CVD, chemotherapy with CVD; DA, dopamine; f, female, L, left; LOM, location of metastases; LOP, location of primary; Lu, lungs; m, male; Me, mediastinum, MIBG, $^{131}$I-MIBG treatment; Mtt, methoxytyramine, Ne, neck; NE, norepinephrine; NMN, normetanephrine; no, number; Pat., patient; R, right; Res, surgical resection; RT, radionuclide therapy; TTM, time to metastases (years).

Table 2: Number of identified lesions in $^{68}$Ga-DOTATATE, $^{18}$F-FDA-, $^{18}$F-FDOPA-, $^{18}$F-FDG-PET/CT, and CT/MRI compared to lesions identified by the imaging comparator.

<table>
<thead>
<tr>
<th>Lesions</th>
<th>$^{68}$Ga-DOTATATE</th>
<th>$^{18}$F-FDG</th>
<th>$^{18}$F-FDOPA</th>
<th>$^{18}$F-FDA</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All compartments</td>
<td>285/289</td>
<td>248/289</td>
<td>175/285</td>
<td>148/285</td>
<td>245/289</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>65/65</td>
<td>57/65</td>
<td>39/65</td>
<td>39/65</td>
<td>55/65</td>
</tr>
<tr>
<td>Lungs</td>
<td>62/63</td>
<td>45/63</td>
<td>45/63</td>
<td>18/63</td>
<td>62/63</td>
</tr>
<tr>
<td>Abdomen</td>
<td>43/43</td>
<td>40/43</td>
<td>31/43</td>
<td>19/43</td>
<td>33/43</td>
</tr>
<tr>
<td>Liver</td>
<td>5/5</td>
<td>3/5</td>
<td>4/5</td>
<td>0/5</td>
<td>5/5</td>
</tr>
<tr>
<td>Bone</td>
<td>95/98</td>
<td>91/98</td>
<td>41/94</td>
<td>57/94</td>
<td>82/98</td>
</tr>
</tbody>
</table>

Table 3: Detection rate (%) and 95% CI (%) for $^{68}$Ga-DOTATATE, $^{18}$F-FDA-, $^{18}$F-FDOPA-, $^{18}$F-FDG-PET/CT, and CT/MRI.

<table>
<thead>
<tr>
<th>Detection rate</th>
<th>$^{68}$Ga-DOTATATE</th>
<th>$^{18}$F-FDG</th>
<th>$^{18}$F-FDOPA</th>
<th>$^{18}$F-FDA</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All compartments</td>
<td>98.6 (96.5 to 99.5)</td>
<td>85.8 (81.3 to 89.4)</td>
<td>61.4 (55.6 to 66.9)</td>
<td>51.9 (46.1 to 57.7)</td>
<td>84.8 (80.0 to 88.5)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>100 (94.4 to 100)</td>
<td>87.7 (77.6 to 93.6)</td>
<td>60.0 (47.9 to 71.0)</td>
<td>60.0 (47.9 to 71.0)</td>
<td>84.6 (73.9 to 91.4)</td>
</tr>
<tr>
<td>Lungs</td>
<td>98.4 (92.5 to 99.7)</td>
<td>71.4 (59.3 to 81.1)</td>
<td>71.4 (59.3 to 81.1)</td>
<td>28.6 (18.9 to 40.7)</td>
<td>98.4 (91.5 to 99.7)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>100 (91.8 to 100)</td>
<td>93.0 (81.4 to 97.6)</td>
<td>72.1 (57.3 to 83.3)</td>
<td>44.2 (30.4 to 58.9)</td>
<td>76.7 (62.3 to 88.7)</td>
</tr>
<tr>
<td>Liver</td>
<td>100 (56.5 to 100)</td>
<td>60.0 (23.1 to 88.2)</td>
<td>80.0 (37.6 to 96.4)</td>
<td>0% (0.0 to 43.5)</td>
<td>100 (56.5 to 100)</td>
</tr>
<tr>
<td>Bone</td>
<td>96.9 (91.4 to 99.0)</td>
<td>92.9 (86.0 to 96.5)</td>
<td>43.6 (34.0 to 53.7)</td>
<td>60.6 (50.5 to 69.9)</td>
<td>83.7 (75.1 to 89.7)</td>
</tr>
</tbody>
</table>
FIGURES

**Figure 1:** Identified lesions (positive columns) and missed lesions (negative columns) for CT/MRI, $[^{18}\text{F}]-\text{FDG}$, $[^{68}\text{Ga}]-\text{DOTATATE}$, $[^{18}\text{F}]-\text{FDOPA}$, and $[^{18}\text{F}]-\text{FDA}$ PET/CT.

**Figure 2:** 24-year-old female patient with metastatic paraganglioma and $SDHB$ mutation, first diagnosed with left carotid body tumor, lung and bone metastases in 2011. $[^{68}\text{Ga}]-\text{DOTATATE}$ PET (A) demonstrated additional lung and bone lesions (arrows), compared to $[^{18}\text{F}]-\text{FDG}$ PET (B) and $[^{18}\text{F}]-\text{FDOPA}$ PET (C). $[^{18}\text{F}]-\text{FDA}$ PET (D) and $[^{123}\text{I}]-\text{MIBG}$ scintigraphy (not shown) were negative.
Figure 1
Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma


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