Superiority of $[^{68}\text{Ga}]-\text{DOTATATE}\text{ PET/CT}$ to Other Functional Imaging Modalities in the Localization of $SDHB$-Associated Metastatic Pheochromocytoma and Paraganglioma

Ingo Janssenv, Elise M. Blanchetv, Karen Adamsv, Clara C. Chenw, Corina M. Millow, Peter Herscovitch, David Taiebq, Electron Kebebew, Hendrik Lehnert, Antonio T. Fojo, and Karel Pacak

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 $[^{68}\text{Ga}]-\text{DOTA}(0)\text{-Tyr(3)}$-octreotate ($[^{68}\text{Ga}]-\text{DOTATATE}$) positron emission tomography/computed tomography (PET/CT) and to evaluate its diagnostic utility in comparison with the currently recommended functional imaging modalities $[^{18}\text{F}]-\text{fluorodopamine} ([^{18}\text{F}]-\text{FDA}), [^{18}\text{F}]-\text{fluorodihydroxyphenylalanine} ([^{18}\text{F}]-\text{FDOPA}), [^{18}\text{F}]-\text{fluoro-2-deoxy-o-glucose} ([^{18}\text{F}]-\text{FDG}) \text{ PET/CT}$ as well as CT/MRI.

Experimental Design: $[^{68}\text{Ga}]-\text{DOTATATE}\text{ PET/CT}$ was prospectively performed in $17$ patients with $SDHB$-related metastatic PHEOs/PGLs. All patients also underwent $[^{18}\text{F}]-\text{FDG} \text{ PET/CT}$ and CT/MRI, with $16$ of the $17$ patients also receiving $[^{18}\text{F}]-\text{FDOPA}$ and $[^{18}\text{F}]-\text{FDA}$ 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: $[^{68}\text{Ga}]-\text{DOTATATE}\text{ PET/CT}$ demonstrated a lesion-based detection rate of $98.6\%$ [95% confidence interval (CI), $96.5\%$–$99.5\%$], $[^{18}\text{F}]-\text{FDG}, ^{[18}\text{F}]-\text{FDOPA}, ^{[18}\text{F}]-\text{FDA}$ PET/CT, and CT/MRI showed detection rates of $85.8\%$ (CI, $81.3\%$–$89.4\%$; $P < 0.01$), $61.4\%$ (CI, $55.6\%$–$66.9\%$; $P < 0.01$), $51.9\%$ (CI, $46.1\%$–$57.7\%$; $P < 0.01$), and $84.8\%$ (CI, $80.0\%$–$88.5\%$; $P < 0.01$), respectively.

Conclusions: $[^{68}\text{Ga}]-\text{DOTATATE}\text{ PET/CT}$ showed a significantly superior detection rate to all other functional and anatomical imaging modalities and may represent the preferred future imaging modality in the evaluation of $SDHB$-related metastatic PHEO/PGL.

See related commentary by Hofman and Hicks, p. 3815

Introduction

Pheochromocytomas/paragangliomas (PHEO/PGL) 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 four subunits of the succinate dehydrogenase ($SDH$) complex (2, 3), fumarate hydratase ($FH$; ref. 4), MYC-associated factor $X$ ($MAX$; ref. 5), and hypoxia-inducible factor $2\alpha$ ($HIF2\alpha$; ref. 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 $[^{111}\text{In}]-\text{metaiodobenzylguanidine (MIBG)}$ and chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD; refs. 10, 11). Surgery and external beam radiotherapy are less commonly used options...
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 [68Ga]-DOTA (0)-Tyr(3)-octreotate ([68Ga]-DOTATATE) PET/CT in patients with metastatic SDHB-related PHEOs/PGLs and demonstrates the superiority of [68Ga]-DOTATATE PET/CT in the detection of metastatic lesions in these patients, compared with other and currently recommended functional imaging modalities. Our results may suggest modifying the functional imaging algorithm for these patients, depending on the clinical setting, which currently places [18F]-fluoro-2-deoxy-D-glucose ([18F]-FDG) PET/CT as the gold standard. Furthermore, our results indicate that peptide receptor radionuclide therapy or treatment with so-called “cold” somatostatin receptor analogues, long-awaited remedies, could be used as new and promising therapeutic options for metastatic SDHB-related PHEOs/PGLs.

In some patients, however, at least 50% of patients with metastatic PHEOs/PGLs, especially those with SDHB mutations, do not benefit from [131I]-MIBG treatment due to a lack of the norepinephrine transporter system, resulting in suboptimal or no [131I]-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 (NET), are known to express somatostatin receptors (SSTR; ref. 13), and new, promising radiolabeled DOTA peptides for SSTR imaging and SSTR-targeting treatment have been developed. Compared with [111In]-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)-octreotate (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 SSTR2 and SSTR3 was recently shown in PHEOs/PGLs with SDH deficiency (16), including SDHB mutations.

DOTA peptides can be labeled with either the diagnostic positron emission tomography (PET) tracer [18F]-Ga or therapeutic β-emitters such as [111In] or [188Re]. On the one hand, they can provide sensitive SSTR imaging, enabling improved anatomic localization using PET/computed tomography (CT) technique (17) compared with SSTR scintigraphy. On the other hand, when bound to therapeutic β-emitters, they can be, 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).

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 [68Ga]-DOTA (0)-Tyr(3)-octreotate ([68Ga]-DOTATATE) PET/CT in patients with metastatic SDHB-related PHEOs/PGLs and demonstrates the superiority of [68Ga]-DOTATATE PET/CT in the detection of metastatic lesions in these patients, compared with other and currently recommended functional imaging modalities. Our results may suggest modifying the functional imaging algorithm for these patients, depending on the clinical setting, which currently places [18F]-fluoro-2-deoxy-D-glucose ([18F]-FDG) PET/CT as the gold standard. Furthermore, our results indicate that peptide receptor radionuclide therapy or treatment with so-called “cold” somatostatin receptor analogues, long-awaited remedies, could be used as new and promising therapeutic options for metastatic SDHB-related PHEOs/PGLs.

The present study had two main aims: first, to evaluate [68Ga]-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 [68Ga]-DOTATATE PET/CT in comparison with other well-established and currently recommended functional imaging studies in PHEOs/PGLs (20), including [18F]-fluorodopamine ([18F]-FDA), [18F]-fluorodihydroxyphenylalanine ([18F]-FDOPA), [18F]-fluoro-2-deoxy-o-glucose ([18F]-FDG) PET/CT, and in comparison with CT/MRI. Because histologic proof was not possible in many metastatic lesions, the composite of both anatomic and all functional imaging tests was considered the imaging comparator.

Patients and Methods

Patients

Between January and December 2014, 17 consecutive patients (11 men and 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 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.

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 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 3 mm for all neck studies and 6 mm for chest, abdominal, and pelvic scans. Pre- and postinjection 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 [68Ga]-DOTATATE, [18F]-FDG PET/CT scanning, and CT/MRI, with 16 also receiving [18F]-FDOPA and [18F]-FDA PET/CT scans.

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PET/CT scans from the upper thighs to the skull were performed 60 minutes after i.v. injection of a mean administered activity of 201.8 ± 39.6 MBq [68Ga]-DOTATATE, 60 minutes after 362.8 ± 112 MBq [18F]-FDG, 30 minutes after 458.5 ± 83.1 MBq [18F]-FDOPA, and approximately 8 minutes after 57.2 ± 1.1 MBq [18F]-FDG. Sixty minutes before each [18F]-FDOPA scan, 200 mg of carboplatin was 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 a three-dimensional matrix using an iterative algorithm provided by the manufacturer, which also uses time of flight. Low-dose CT studies for attenuation correction and anatomic coregistration were performed without contrast and used for anatomical localization only.

Analysis of data

[68Ga]-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 (SUVmax) were determined, and focal areas of abnormal uptake showing a higher SUVmax 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 [68Ga]-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 ± 5 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.

Statistical analysis

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

Results

[68Ga]-DOTATATE PET/CT had a lesion-based detection rate of 98.6% (CI, 96.5%–99.5%), identifying 285 of 289 lesions (mean SUV 56.0 ± 62.1) compared with our defined imaging comparator. Significantly more lesions were identified on [68Ga]-DOTATATE PET/CT than on all other used functional imaging modalities and CT/MRI (two-sided P < 0.01 for each imaging modality compared with [68Ga]-DOTATATE PET/CT; corresponding cross tables in Supplementary Fig. S1). Lesion-based findings on [68Ga]-DOTATATE PET/CT compared with all other used functional imaging modalities and CT/MRI are summarized and outlined in Tables 2 and 3 as well as in Fig. 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 [18F]-FDA and [18F]-FDG PET/CT, and one lung lesion, which was positive on [18F]-FDG PET/CT and anatomic imaging, were not identified by [68Ga]-DOTATATE PET/CT. A lesion-based evaluation excluding the patient who only received [68Ga]-DOTATATE, [18F]-FDG PET/CT, and CT/MRI did not lead to any statistical change.

Besides the 285 lesions confirmed by the defined imaging comparator, [68Ga]-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/MR, 8 lesions were reported, which were not positive on any functional imaging study. Two were retroperitoneal lymphatic nodes (1.3 cm and 1.6 cm), 4 were in the lungs (0.4–0.8 cm), and two in the liver (0.7 cm and 0.8 cm). Three mediastinal lesions were only positive in [18F]-FDG PET/CT. Not a single lesion was only positive in either [18F]-FDOPA or [18F]-FDA PET/CT but not another functional or anatomic imaging test.

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

The per region detection rate for [68Ga]-DOTATATE was 100%, identifying 42 of 42 regions (42/42); CI, 91.6%–100%, 97.6% for [18F]-FDG (41/42); CI, 87.7%–99.5%, 65.9% for [18F]-FDOPA (27/41); CI, 50.6%–78.4%, 58.4% for [18F]-FDG PET/CT (24/41); CI, 43.4%–72.2%, and 95.2% for CT/MRI (40/42), CI, 84.2%–98.7%.

A PET-imaging example comparing [68Ga]-DOTATATE, [18F]-FDG, [18F]-FDOPA, and [18F]-FDA PET/CT is shown in Fig. 2.

### Discussion

In this study, we evaluated [68Ga]-DOTATATE PET/CT in a cohort of patients with SDHB-related metastatic PHEOs/PGLs in comparison with [18F]-FDA, [18F]-FDOPA, [18F]-FDG PET/CT, and CT/MRI. The composite of both anatomical and all functional imaging tests was considered the imaging comparator.

[68Ga]-DOTATATE PET/CT demonstrated a lesion-based detection rate of 98.6% (CI, 96.5%–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 that 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. [18F]-FDA and [123I]-MIBG specifically target catecholamine synthesis, storage, and secretion pathways, and both enter the cell via the norepinephrine transporter (21, 22). In this study, [18F]-FDA had a low lesion-based detection rate of 51.9% (CI, 46.1%–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 [123I]-MIBG negativity of more than 50% of patients in SDHB mutation–associated PHEOs/PGLs (12). Six of the patients in our study had undergone [123I]-MIBG scintigraphy with a very low lesion detection rate of 18.7% (CI, 12.0%–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 that enters the cell via glucose transporters (GLUT; ref. 26). Its accumulation is related to increased glucose metabolism as seen in the succinate dehydrogenase complex II subunit B can lead to a downregulation of the 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; ref. 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%–89.4%) for [18F]-FDG PET/CT.

With a lesion-based detection rate of 98.6% (CI, 96.5%–99.5%), [68Ga]-DOTATATE PET/CT was significantly superior to all other functional imaging modalities in this study.

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### Table 2. Number of identified lesions in [68Ga]-DOTATATE, [18F]-FDA, [18F]-FDOPA, [18F]-FDG-PET/CT, and CT/MRI compared with lesions identified by the imaging comparator.

<table>
<thead>
<tr>
<th>Lesions</th>
<th>[68Ga]-DOTATATE</th>
<th>[18F]-FDG</th>
<th>[18F]-FDOPA</th>
<th>[18F]-FDG-PET/CT</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>45/43</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>

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### Table 3. Detection rate (%) and 95% CI (%) for [68Ga]-DOTATATE, [18F]-FDA, [18F]-FDOPA, [18F]-FDG-PET/CT, and CT/MRI.

<table>
<thead>
<tr>
<th>Detection rate</th>
<th>[68Ga]-DOTATATE</th>
<th>[18F]-FDG</th>
<th>[18F]-FDOPA</th>
<th>[18F]-FDG-PET/CT</th>
<th>CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All compartments</td>
<td>98.6 (96.5–99.5)</td>
<td>85.8 (81.3–89.4)</td>
<td>61.4 (55.6–66.9)</td>
<td>51.9 (46.1–57.7)</td>
<td>84.8 (80.0–88.5)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>98.4 (95.5–99.7)</td>
<td>71.4 (59.3–81.1)</td>
<td>71.4 (59.3–81.1)</td>
<td>28.6 (18.9–40.7)</td>
<td>98.4 (95.5–99.7)</td>
</tr>
<tr>
<td>Lungs</td>
<td>98.4 (92.5–99.7)</td>
<td>85.8 (81.3–89.4)</td>
<td>61.4 (55.6–66.9)</td>
<td>51.9 (46.1–57.7)</td>
<td>84.8 (80.0–88.5)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>96.9 (91.4–99.0)</td>
<td>92.9 (86.0–98.5)</td>
<td>43.6 (34.0–53.7)</td>
<td>60.6 (50.5–69.9)</td>
<td>83.7 (75.1–89.7)</td>
</tr>
<tr>
<td>Liver</td>
<td>98.6 (96.5–99.5)</td>
<td>85.8 (81.3–89.4)</td>
<td>61.4 (55.6–66.9)</td>
<td>51.9 (46.1–57.7)</td>
<td>84.8 (80.0–88.5)</td>
</tr>
</tbody>
</table>

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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 [111In]-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 has 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 [68Ga]-DOTATATE and [68Ga]-DOTATOC PET/CT, approaching or reaching 100% (17, 34).

Besides its diagnostic value, [68Ga]-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). Although 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 FDA at present. In the meanwhile, the high sensitivity of [68Ga]-DOTATATE PET/CT in SDHB-related metastatic PHEO/PGL suggests that these patients can be treated with cold SSTR analogues, 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 (especially skull base) cannot be accessed by any surgical approach.

The phenomenon of additional lesions appearing with [68Ga]-DOTA analogues PET/CT that were not seen by other imaging studies has been reported before (15, 17). Because 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, studies have also reported histologic confirmation of SSTR-positive tumor tissue in such cases, which led to a treatment change in up to 60% of patients (39).

Finally, the high detection rate of [68Ga]-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 [68Ga]-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 [68Ga]-DOTA peptides into consideration, [18F]-FDG is recommended as first-line functional imaging of SDHB-related PHEOs/PGLs (20). However, our results indicate that [68Ga]-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 [68Ga]-DOTATATE PET/CT, 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 [68Ga]-DOTATATE PET/CT is still unclear and has to be evaluated. In clinical settings of doubtful CT/MRI results, [68Ga]-DOTATATE might also be helpful, although potential false-positive results could occur. The more specific functional imaging studies such as [18F]-FDOPA and [18F]-FDA PET/CT seem to harbor a higher risk for false-negative results. Finally, [18F]-FDOPA PET/CT and especially [18F]-FDA PET/CT are of limited availability, whereas for [68Ga]-DOTATATE PET/CT, we believe that 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 the one hand, cannot fully exclude false-positive results (e.g., possible positive lesions in [68Ga]-DOTATATE PET/CT, [18F]-FDG-PET/CT, and/or CT/MRI related to inflammation or possible positive lesions in [68Ga]-DOTATATE PET/CT, [18F]-FDOPA PET/CT, and/or CT/MRI related to different NETs). 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 [18F]-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 [68Ga]-DOTATATE PET/CT in these patients, particularly in the detection of progressive metastatic disease, additional disease sites, and even early detection of metastatic disease. [68Ga]-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 [68Ga]-DOTATATE PET/CT in other genotypes, sporadic PHEO/PGL, or for treatment monitoring should be evaluated soon.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.
Authors’ Contributions

Conception and design: I. Janssen, E.M. Blanchet, C.M. Millo, H. Lehnert, K. Pacak
Development of methodology: E.M. Blanchet, C.M. Millo, P. Herscovich, K. Pacak
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): I. Janssen, K. Adams, C.C. Chen, P. Herscovich, E. Kebebew, A.T. Fojo, K. Pacak
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I. Janssen, C.M. Millo, D. Taieb, E. Kebebew, H. Lehnert, A.T. Fojo, K. Pacak
Writing, review, and/or revision of the manuscript: I. Janssen, E.M. Blanchet, C.C. Chen, C.M. Millo, P. Herscovich, D. Taieb, E. Kebebew, H. Lehnert, K. Pacak
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): C.C. Chen, K. Pacak
Study supervision: C.M. Millo, K. Pacak

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