**18F-FDOPA PET/CT Imaging of MAX-Related Pheochromocytoma**

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**Context:** MYC-associated factor X (MAX) has been recently described as a new susceptibility pheochromocytoma (PHEO) gene with a total of ~40 reported cases. At present, no study has specifically described the functional imaging phenotype of MAX-related PHEO.

**Objective, Patients, and Design:** The objective of the present study was to present our experience with contrast-enhanced computed tomography (CT) and 18F-fluorodihydroxyphenylalanine (18F-FDOPA) positron emission tomography (PET)/CT in six consecutive patients (four at the initial diagnosis and two at the follow-up evaluation) with rare, but clinically important, MAX-related PHEOs. In five patients, 18F-FDOPA was also compared with other radiopharmaceutical agents.

**Results:** The patients had five different mutations in the MAX gene that caused disruption of Max/Myc interaction and/or abolished interaction with DNA based on in silico analyses. All but one patient developed bilateral PHEOs during their lifetime. In all cases, 18F-FDOPA PET/CT accurately visualized PHEOs that were often multiple within the same gland or bilaterally and detected more adrenal and extra-adrenal lesions than did CT (per-lesion sensitivity, 90.9% vs 52.4% for CT/magnetic resonance imaging). The two PHEOs missed on 18F-FDOPA PET/CT were 1 cm, corresponding to nodular adrenomedullary hyperplasia. 68Ga-DOTA,Tyr3-octreotate PET/CT detected fewer lesions than did 18F-FDOPA PET/CT in one of three patients, and 18F-fluorodeoxyglucose PET/CT was only faintly positive in two of four patients with underestimation of extra-adrenal lesions in one patient.

**Abbreviations:** 3D, three-dimensional; 18F-FDG, 18F-fluorodeoxyglucose; 18F-FDOPA, 18F-fluorodihydroxyphenylalanine; 68Ga-DOTATATE, 68Ga-DOTA,Tyr3-octreotate; 123I-MIBG, 123I-metaiodobenzylguanidine; Adx, adrenalectomy; CT, computed tomography; MAX, MYC-associated factor X; MEN2, multiple endocrine neoplasia type 2; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; NIH, National Institutes of Health; PGL, paraganglioma; PET, positron emission tomography; PHEO, pheochromocytoma; PPGL, pheochromocytoma and paraganglioma together; SDH, succinate dehydrogenase.
Conclusions: MAX-related PHEOs exhibit a marked 18F-FDOPA uptake, a finding that illustrates the common well-differentiated chromaffin pattern of PHEOs associated with activation of kinase signaling pathways. 18F-FDOPA PET/CT should be considered as the first-line functional imaging modality for diagnostic or follow-up evaluations for these patients. (J Clin Endocrinol Metab 103: 1574–1582, 2018)

Materials and Methods

Patients

Six patients with germline mutation in the MAX gene [c.172-3C>G; c.97C>T (n = 2); c.155 C>G; c.199A>G; c.1_171del] were evaluated by 18F-FDOPA PET/CT at two academic endocrine tumor centers [La Timone University Hospital and the National Institutes of Health (NIH)].

At La Timone University Hospital, 18F-FDOPA PET/CT is used in the setting of marketing authorization. In keeping with local institutional guidelines, all patients gave informed consent for the use of anonymous personal data to be extracted from their medical records for scientific purposes. At the NIH, the Eunice Kennedy Shriver National Institute of Child Health and Human Development/NIH institutional review board approved the study, which was performed under protocol 00-CH-0093 (ClinicalTrials.gov identifier, NCT00004847).

18F-FDOPA PET/CT imaging protocol

All 18F-DOPA PET/CT scans of the patients studied at La Timone University Hospital (patients 1 to 3) were performed using a combined PET/CT device (Discovery 710; GE Healthcare). Patients fasted for ≥3 hours before tracer injection. In these patients, 3 to 4 MBq/kg of 18F-DOPA was intravenously injected without carbidopa premedication. The acquisition protocol included a delayed whole-body acquisition from the top of the skull to the upper thigh (2.5 minutes per bed position) starting at ~60 minutes after injection. CT studies for attenuation correction and anatomical registration were performed without administration of contrast medium. The PET data were reconstructed iteratively. CT, PET (after attenuation correction), and fused PET/CT images were displayed on a dedicated workstation for analysis. Each focus of increased extrapulmonary radionuclide uptake was recorded and interpreted according to the particular case.

The 18F-DOPA PET/CT scans of the three patients at the NIH (patients 4 to 6) were performed using a combined PET/CT device (Siemens Biograph-mCT 64; Siemens Healthineers USA). The patients fasted for 6 hours before tracer injection. The 18F-FDOPA PET/CT scans were performed 30 minutes after injection of a mean administered activity of 463.4 ± 9.5 MBq with oral administration of 200 mg of carbidopa 60 minutes before tracer injection. The acquisition protocol included a delayed whole-body acquisition from the top of the skull to the upper thigh (5.0 minutes per bed position) starting at ~30 minutes after injection. The PET images were reconstructed using an iterative algorithm provided by the manufacturer, which also uses point spread function and time of flight. Low-dose CT studies for attenuation correction and anatomical coregistration were performed without contrast. CT, PET (after attenuation correction), and fused PET/CT images were displayed on a dedicated workstation for analysis. Each focus of increased extrapulmonary radionuclide uptake was recorded and interpreted according to the particular case.

Although ~20% to 24% of apparently sporadic pheochromocytomas (PHEOs) are caused by germline mutations (1), patients with bilateral PHEOs and/or those with a family history most likely carry such mutations. Among the PHEO susceptibility genes, recently, MYC-associated factor X (MAX) has been identified as another PHEO gene (2, 3). Compared with other hereditary PHEOs and paragangliomas (PGLs), these tumors are very rare, with ~40 cases reported to date (2, 4–8). The pathogenic germline MAX variant was found in 19 of 1694 index patients with PHEOs and PGLs occurring together [PPGLs (1.12%)] without mutations in major PPGL susceptibility genes (RET, VHL, SDHB, SDHC, SDHD, and TMEM127) (4). All 19 index patients had adrenal tumors, including 13 (68.4%) with either bilateral or multiple PHEOs within the same gland; 16% (n = 3) developed additional tumors at thoracoabdominal sites, and 37% (n = 7) had a family history of PPGLs (4).

Tumorigenesis is likely related to a loss of transcriptional repression of MAX on MYC transcriptional activity (9). Rarely, these patients will develop renal oncocytoma (10). These tumors are moderately associated with metastatic disease (4). The median age at the diagnosis of MAX-related PHEO is 34 years.

The role of anatomical and functional imaging in PPGLs is to detect the location (adrenal vs extra-adrenal tumors), multiplicity, recurrence, and the presence or absence of metastases. In recent years, functional imaging, represented mainly by positron emission tomography (PET), has gained an increasing role in PPGL staging and restaging, with PET/computed tomography (CT) was found to be a useful radionuclide imaging modality, and, therefore, it was used in a small series of six patients with MAX mutations. The aim of the present study was to describe the value of 18F-FDOPA PET/CT in the detection of primaries and metastases in these rare, but clinically important, tumors.
In silico homology modeling

The three-dimensional (3D) crystal structure of Myc-Max heterodimers bound to their common DNA target (PubMed identifier, 12553908; protein data bank code, 1NKP) was used as template to build 3D models of the different mutants (15). Variants c.97C>T and c.155C>G introduce a stop signal at position R33 and S52, respectively. The 3D models were therefore generated by discarding all C-terminal residues after the stop codon in the 3D structure. Variant c.172-3C>G leads to an alternate splicing at residue Ala58 and a stop codon after Ser64. In this case, the 3D model was generated using modeler homology modeling program (PubMed identifier, 27801516). The 3D model for the deletion mutant IVS1-IVS3del was generated by removing Max residues 1 to 57 in the X-ray 3D structure.

Analysis of data

All PET/CT images were interpreted by experienced nuclear medicine physicians, and all CT and magnetic resonance imaging (MRI) studies were interpreted by experienced radiologists, who were unaware of all other imaging and clinical data, except for the initial diagnosis, sex, and age of the patient.

Maximal standardized uptake values were determined from the PET images. Focal areas of nonphysiological increased radiotracer activity with a higher maximal standardized uptake value than the surrounding tissue were considered to indicate lesions.

A patient was considered to have positive findings regardless of the number of positive lesions present. Using all imaging studies, patient-to-patient and lesion-to-lesion analyses were performed and compared.

Reference standard

The histological findings were considered the reference standard for the diagnosis of PPGL. In cases in which no surgical resection had been performed, PPGL was diagnosed by comparing the findings from the different imaging modalities and by reaching a consensus between the experienced radiologists and nuclear medicine physicians. Malignancy was defined only by the presence of metastatic lesions at sites where chromaffin cells are normally absent (i.e., bones and lymph nodes).

Results

Patients

Six consecutive patients (one female and five males; median age, 37.5 years; range, 21 to 56) with a MAX mutation were evaluated using 18F-DOPA PET/CT. Two of the six patients had a family history of PHEO, and one of the six had a likely family history of PHEO (represented by acute coronary syndrome in the patient’s sister at age 20 years). The patients had five different mutations in the MAX gene that caused disruption of Max/Myc interaction and/or abolished interaction with DNA based on in silico analyses (Fig. 1). Variants c.97C>T, c.155C>G, and c.172-3C>G introduce a premature stop codon inducing the complete loss of the Max C-terminal alpha helix. These truncation mutations result in disruption of the Max/Myc interaction. In contrast, for c.1_171del (loss of the Max N-terminal alpha helix), most residues in contact with Myc in the wild-type structure are not affected by the deletion, with a probable preservation of a weakened Max/Myc interaction. However, it has been shown that positively charged residues of Max (Arg35, Arg36, and Arg60 and Lys40) play a major role in the interaction with negatively charged DNA (16). Max c.97C>T and c.1_171del variants are lacking all four and three of these four residues, respectively. Therefore, the interaction with DNA is most probably completely abolished for these variants. In the case of c.155C>G and c.172-3C>G Max variants, only Arg60 is missing, which should also lead to reduced DNA binding (Fig. 1).

At 18F-DOPA PET/CT imaging, four patients underwent evaluation for the initial diagnosis and two patients had a history of adrenalectomy (Adx): one, bilateral Adx and one, unilateral Adx. Each patient underwent at least contrast-enhanced CT with other radiopharmaceutical agents. The other radiopharmaceutical agents included 123I-metaiodobenzylguanidine (123I-MIBG; n = 2) scintigraphy and 18F-fluorodeoxyglucose (18F-FDG) PET/CT (n = 4) and 68Ga-DOTA,Tyr3-octreotate (68Ga-DOTATATE; n = 3) PET/CT. The clinical characteristics of the patients are summarized in Table 1.

18F-DOPA PET/CT findings

All patients (patients 1 to 4) who presented before surgery had nonmetastatic primary MAX-related PHEOs and three had bilateral PHEOs (patients 1 to 3), some with multiple foci of uptake within both adrenal glands (Fig. 2). In all cases, uptake foci were clearly distinguishable from the extranodular adrenal uptake. Finally, the degree of adrenal involvement (unilateral vs bilateral; number of tumors per gland) in these three cases was better characterized and delineated by 18F-DOPA PET/CT than by contrast-enhanced CT (Table 1). In patient 4, anatomical imaging (CT and MRI) and 18F-DOPA PET/CT were concordant for a single left adrenal mass in the diagnosis of PHEO. However, in patient 5, anatomical imaging and 18F-DOPA PET/CT were discordant for a single left adrenal nodule; thus, adrenal adenoma was diagnosed from the anatomical imaging findings but PHEO was diagnosed from the 18F-DOPA PET/CT findings. In patient 6, the number of extra-adrenal lesions was underestimated on CT (Tables 1 and 2).

Comparison between 18F-DOPA PET/CT and other functional imaging modalities

In patient 1, the PHEOs were not seen on axial 18F-FDG PET/CT scans owing to the increased activation of brown adipose tissue in periadrenal and perirenal areas
that was observed and attributed to the high levels of norepinephrine (Supplemental Fig. 1). In patient 3, 123I-MIBG scintigraphy was performed and showed a bilateral tracer uptake (data not shown). In patients 4 and 5, concordance was found between the 18F-FDOPA and 68Ga-DOTATATE PET/CT findings in the detection of a left PHEO; however, 18F-FDG PET/CT was faintly positive for patient 4 and negative for patient 5 (Fig. 3; Table 2). In patient 6, two of the five lesions seen on 18F-FDOPA PET/CT were also seen on 68Ga-DOTATATE PET/CT. In contrast, 18F-FDG PET/CT showed only one lesion (Fig. 4; Table 2).

**Per-patient and per-lesion detection rates**

The per-patient detection rates for MAX-related PPGLs using 18F-DOPA PET/CT (six of six), 68Ga-DOTATATE PET/CT (three of three), 18F-FDG PET/CT (two of four), and CT/MRI (five of six) was 100%, 100%, 100%, 50.0%, and 85.7%, respectively (Supplemental Table 1).

The detection rate for MAX-related PHEOs using 18F-FDOPA PET/CT (15 of 17), 68Ga-DOTATATE PET/CT (2 of 2), 18F-FDG PET/CT (1 of 6), and CT/MRI (9 of 16) was 88.2%, 100%, 16.7%, and 56.3%, respectively. The per-lesion detection rate for 18F-FDOPA PET/CT (20 of 22), 68Ga-DOTATATE PET/CT (4 of 7), 18F-FDG PET/CT (2 of 11), and CT/MRI (11 of 21) was 90.9%, 57.1%, 18.2%, and 52.4%, respectively, in the identification of MAX-related PPGLs (Table 2).

**Discussion**

Our results have demonstrated that 18F-FDOPA PET/CT represents a very sensitive imaging tool in the evaluation of MAX-related PHEOs at the initial diagnosis or during follow-up. All but one patient had disease limited to the adrenal gland. In that patient (patient 6), multiple uptake foci were located in the retroperitoneum, which could have been related to either extra-adrenal PGLs and/or lymph node metastases. The 18F-FDOPA PET/CT findings also provided a more comprehensive picture of the disease with identification of bilateral adrenal involvement in three patients (patients 1 to 3). They all underwent total unilateral or bilateral Adx owing to the...
widespread adrenal involvement by multiple tumors (PHEO or nodular adrenomedullary hyperplasia) in most patients. Because of the high frequency of PHEO multicentricity, it could be anticipated that if subtotal Adx is performed, it could potentially be associated with earlier tumor recurrence than that in MEN2 patients who mainly harbor a prominent PHEO associated with diffuse or micronodular adrenomedullary hyperplasia (17). Furthermore, the greater risk of malignancy in MAX-related PHEOs compared with MEN2 PHEOs favors performing total instead of subtotal Adx; however, this requires a consensus among the interdisciplinary management teams until an expert consensus statement has been formulated.

Among the five identified mutations, four (c.155C>G, c.172-3C>G, c.199A>C, and c.1_171del) have not been previously reported. Molecular modeling using known 3D structures showed a major impact on Max structure for the different variants. *In silico* studies predicted the disruption of the interaction between Max and Myc for

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Age, y/Sex at Presentation for 18F-FDOPA PET/CT</th>
<th>History</th>
<th>Family History of PHEO</th>
<th>Plasma-Free NMN (Fold URL)</th>
<th>Plasma-Free MN (Fold URL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>21/M</td>
<td>Hypertensive crisis with chest pain</td>
<td>None</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>2</td>
<td>25/M</td>
<td>Chest pain</td>
<td>Yes, father with PHEO</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>43/M</td>
<td>20-y History of hypertension, hypertensive crisis, chest pain, and sweating</td>
<td>Possibly sister (acute coronary syndrome at 20 y)</td>
<td>8</td>
<td>1.3</td>
</tr>
<tr>
<td>4</td>
<td>59/M</td>
<td>Severe headache, palpitation, sweating, and hypertension</td>
<td>None</td>
<td>7.7</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5</td>
<td>37/F</td>
<td>R Adx (at 37 y), sweating, and abdominal pain</td>
<td>None</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6</td>
<td>38/M</td>
<td>R Adx (at 27 y), L Adx (at 31 y), resection retrocaval PGL (at 32 y), and sweating</td>
<td>Yes, father and paternal uncle</td>
<td>2.9</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

(Continued)
most variants. Furthermore, the interaction with DNA is predicted to be reduced or abolished for these variants.

To the best of our knowledge, ours is the first study to specifically describe the results of imaging findings in MAX patients. The 18F-FDOPA tumor/background uptake ratio was very high, leading to clear visualization within the same glands in MAX patients. The absence of intense diffuse uptake by the adrenomedullary gland is a clear advantage over 123I-MIBG. This 18F-FDOPA imaging phenotype of MAX-related PHEO is very similar to the imaging features described in MEN2 and NF1 patients. In addition to several clinicopathologic differences between MAX and MEN2/NF1 patients (for MAX, a greater malignancy risk, a mixed norepinephrine/epinephrine secretory profile, possible extra-adrenal involvement, absence of syndromic manifestations), all these tumors are linked to activation of kinase signaling pathways (18). The high 18F-FDOPA uptake pattern is probably linked to the well-differentiated pattern of these tumors compared with those related to succinate dehydrogenase (SDH) deficiency and associated with a hypermethylated profile with subsequent silencing of key genes involved in neuroendocrine differentiation (19).

Although in our study only a few patients were evaluated using 68Ga-DOTATATE (a somatostatin receptor subtype 2 analog) and 18F-FDG (an 18F-labeled glucose analog), we found clear superiority for 18F-FDOPA compared with these other PET radiopharmaceuticals. 18F-FDG PET/CT was only slightly positive for PHEO detection in one of three patients (33.3%) and PPGL detection in two of four patients (50.0%), and its reliability was affected by brown adipose tissue activation (patient 1; 2).

### Table 1. Continued

<table>
<thead>
<tr>
<th>Contrast-Enhanced CT Findings (cm)</th>
<th>18F-FDOPA PET/CT Findings</th>
<th>Treatment</th>
<th>Pathological Findings</th>
<th>MAX Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral adrenal nodules (L: 3.3 and 2.7)</td>
<td>Bilateral uptake foci (3 L; 1 R)</td>
<td>L Adx</td>
<td>4 PHEOs (3 PHEO and 1 micro-PHEO); PASS score 4, Ki-67 = 5% for all; negative MAX staining</td>
<td><strong>c.172-3C&gt;G</strong></td>
</tr>
<tr>
<td>Bilateral adrenal nodules (L: 1.8; R: 1.6)</td>
<td>Bilateral uptake foci (2 L; 2 R)</td>
<td>Bilateral Adx</td>
<td>4 PHEOs (2 L, 2 R); PASS score 1, Ki-67 &lt;1%; negative MAX staining</td>
<td><strong>c.97C&gt;T</strong></td>
</tr>
<tr>
<td>Bilateral adrenal nodules (L: 2.4, 1.8, and 1; R: 3.7 and 1.7)</td>
<td>Bilateral uptake foci (3 L; 2 R)</td>
<td>Bilateral Adx</td>
<td>6 PHEOs (2 L, 2 micro-PHEO, 1 R PHEO, 1 R micro-PHEO); PASS score 1, Ki-67 &lt;1% for all PHEOs; negative MAX staining</td>
<td><strong>c.155 C&gt;G</strong></td>
</tr>
<tr>
<td>Unilateral adrenal mass (L: 5.4)</td>
<td>Unilateral peripheral uptake foci with central photopenia (1 L)</td>
<td>L Adx</td>
<td>1 PHEO (1 L PHEO); PASS score 8; Ki-67 = 2%; negative MAX staining</td>
<td><strong>c.199A&gt;C</strong></td>
</tr>
<tr>
<td>Unilateral adrenal nodule (L: 1.6)</td>
<td>Unilateral uptake foci (1 L)</td>
<td>Wait and watch</td>
<td>Initial surgery: 2R PHEOs; PASS Score 6; Ki-67 &lt;1%</td>
<td><strong>c.1..171del</strong></td>
</tr>
<tr>
<td>2 foci (R retroperitoneal in adrenal fossa: 0.9; aorto caval: 1.1)</td>
<td>5 foci of uptake in retroperitoneum</td>
<td>Wait and watch</td>
<td>Previous surgeries: 1 R PHEO; PASS score 3, Ki-67 &lt;1%; 1 L PHEO; PASS score 2, Ki-67 &lt;1%; 1 retrocaval PCL, Ki-67 = 2%</td>
<td><strong>c.97C&gt;T (p.Arg33X)</strong></td>
</tr>
</tbody>
</table>

Abbreviations: Adx, adrenalectomy; F, female; Ki-67, Ki-67 (i.e., MIB-1) labeling index on immunohistochemistry; L, left; M, male; MN, metanephrine; NMN, normetanephrine; PASS score, pheochromocytoma of the adrenal gland scaled score; Pt., patient; R, right; URL, upper reference limit.

### Table 2. Lesion Detection Rates of 18F-DOPA PET/CT, 68Ga-DOTATATE PET/CT, 18F-FDG PET/CT, and CT/MRI in MAX-related PPGLs

<table>
<thead>
<tr>
<th>Pt. No.</th>
<th>Adrenal Total</th>
<th>Adrenal Total</th>
<th>Adrenal Total</th>
<th>Adrenal Total</th>
<th>Adrenal Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>80 (4/5)</td>
<td>80 (4/5)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0/0)</td>
</tr>
<tr>
<td>2</td>
<td>100 (4/4)</td>
<td>100 (4/4)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0/0)</td>
</tr>
<tr>
<td>3</td>
<td>83 (5/6)</td>
<td>83 (5/6)</td>
<td>NA</td>
<td>NA</td>
<td>0 (0/0)</td>
</tr>
<tr>
<td>4</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
</tr>
<tr>
<td>5</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0/0)</td>
<td>100 (5/5)</td>
<td>0 (0/0)</td>
<td>40 (2/5)</td>
<td>0 (0/0)</td>
</tr>
<tr>
<td>Total</td>
<td>88.2 (15/17)</td>
<td>90.9 (20/22)</td>
<td>100 (2/2)</td>
<td>57.1 (4/7)</td>
<td>16.7 (1/6)</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

Data in parentheses are the number of lesions detected by an imaging modality to the number of lesions detected by the reference standard.
Supplemental Fig. 1) presumably due to highly elevated values of norepinephrine. Regarding 68Ga-DOTATATE, the uptake pattern was lower compared with that of 18F-FDOPA in the two patients evaluated, with inferior lesion detection in one patient (patient 6) with extra-adrenal lesions. In our previous study, we showed that although 68Ga-DOTATATE PET/CT was the most sensitive tool in the detection of head and neck PGLs, it can miss extra-adrenal retroperitoneal PGLs (20). In the detection of non-SDH-deficient metastatic PPGLs, 18F-FDOPA PET/CT was found to be superior to 18F-FDG PET/CT and inferior to 68Ga-DOTATATE PET/CT (21). However, in the detection of SDHB-related metastatic PPGLs (22) 18F-FDOPA PET/CT was inferior to both 68Ga-DOTATATE and 18F-FDG PET/CT, whereas, 18F-FDOPA PET/CT was superior to both 68Ga-DOTATATE and 18F-FDG PET/CT in the detection of PGLs associated with polycythemia-PGL syndromes, irrespective of the

Figure 3. Head to head comparison between 18F-FDOPA, 68Ga-DOTATATE, and 18F-FDG PET/CT with MAX-related PHEOs in two patients: (A–F) patient (Pt.no.) 5 and (G–L) patient 6. Both patients exhibited unilateral PHEOs in the left adrenal gland (arrows). Axial attenuation-corrected (A and G) 18F-FDOPA PET, (B and H) 68Ga-DOTATATE PET, (E and K) 68Ga-DOTATATE PET/CT, (C and I) 18F-FDG PET, and (F and L) 18F-FDG PET/CT images. In patient 4, peripheral uptake with central photopenia was observed in all 18F-FDOPA, 68Ga-DOTATATE, and 18F-FDG PET/CT images. In patient 5, because of the very low uptake pattern on 18F-FDG PET, the findings were read as negative for PHEO in the left adrenal gland.
underlying mutation status (hypoxia-inducible factor 2 alpha and prolyl hydroxylase 1 and 2) (23). However, further studies are needed before providing any firm conclusions regarding PPGLs associated with mutations in RET, NF1, and VHL. The inferior lesion detection using 68Ga-DOTATATE in MAX-related PPGLs suggests that peptide receptor radionuclide therapy using somatostatin receptor agonists might not be suitable for patients with MAX-related metastatic disease.

In conclusion, the present study has shown that MAX-related PHEOs exhibit a marked 18F-FDOPA uptake, a finding that is common to MEN2- and NF1-related PHEOs. Our results are limited by the very low frequency of MAX mutations in the PHEO population, and a more precise description of the imaging metabolic type would require a multinational study. At present, we recommend using 18F-FDOPA as the first-line imaging modality for initial staging or during follow-up evaluations of MAX-mutation carriers.

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Disclosure Summary: The authors have nothing to disclose.

References

