EANM/SNMMI 2019 guidelines for radionuclide imaging of pheochromocytoma and paraganglioma

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**Abbreviations**

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<td>pheochromocytoma and paraganglioma</td>
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<td>HNPGL</td>
<td>head and neck paraganglioma</td>
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<td>RET</td>
<td>rearranged during transfection proto-oncogene</td>
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<td>VHL</td>
<td>von Hippel-Lindau</td>
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<td>SDH</td>
<td>succinate dehydrogenase</td>
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<td>SDHA, SDHB, SDHC, SDHD</td>
<td>succinate dehydrogenase subunits A, B, C, and D</td>
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<td>MAX</td>
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<td>fumarate hydratase</td>
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<td>SSAs</td>
<td>somatostatin analogues</td>
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<td>MIBG</td>
<td>metaiodobenzylguanidine</td>
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<td>RCC</td>
<td>renal cell carcinoma</td>
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<td>GIST</td>
<td>gastrointestinal stromal tumor</td>
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<td>MTC</td>
<td>medullary thyroid carcinoma</td>
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<td>WHO</td>
<td>World Health Organization</td>
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<td>MEN</td>
<td>multiple endocrine neoplasia</td>
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<td>BAT</td>
<td>brown adipose tissue</td>
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<td>NPV</td>
<td>negative predictive value</td>
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<td>PPV</td>
<td>positive predictive value</td>
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<td>NE</td>
<td>norepinephrine</td>
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<td>epinephrine</td>
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<td>DA</td>
<td>dopamine</td>
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<td>NET</td>
<td>neuroendocrine tumor</td>
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<td>GI</td>
<td>gastrointestinal</td>
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<td>SRS</td>
<td>somatostatin receptor scintigraphy</td>
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<td>COMT</td>
<td>catechol-O-methyltransferase</td>
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<td>AADC</td>
<td>aromatic L-amino acid decarboxylase</td>
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Abstract

There are diverse radionuclide imaging techniques available for the diagnosis, staging and follow-up of pheochromocytoma and paraganglioma (PPGL). Beyond their ability to detect and localize disease, these imaging approaches variably characterize these tumors at cellular and molecular levels and can guide therapy. In particular, the excellent results obtained with gallium-68(\(^{68}\text{Ga}\))-labelled somatostatin receptor analogs (SSAs) in recent years have simplified the imaging approach that can also be used for selecting patients for peptide receptor radionuclide therapy (PRRT) as a potential alternative or complement to the traditional theranostic approach with iodine-123(\(^{123}\text{I}\))- or iodine-131(\(^{131}\text{I}\))-labelled meta-iodo-benzyl-guanidine (MIBG). Genomic characterization of subgroups with differing risks of developing lesions and of subsequent metastatic spread are refining the use of molecular imaging for surveillance of patients in combination with catecholamine assays.

The purpose of the present guidelines is to assist nuclear medicine practitioners in selecting, performing, interpreting, and reporting the results of the currently available SPECT and PET imaging procedures. Guidelines from related fields and relevant literature have been taken into consideration in consultation with leading experts involved in the management of PPGL patients. The information provided should be taken in the context of local laws and regulations as well as availability of various radiopharmaceuticals.

Purpose

The purpose of these guidelines is to assist nuclear medicine practitioners in:

1. Understanding the role and challenges of radionuclide imaging of PPGL.
2. Providing practical information for performing different imaging procedures for these tumors.
3. Providing an algorithm for selecting the most appropriate imaging procedure in specific clinical situations.
Background information and definitions

Tumor origin and location

Pheochromocytoma (PHEO) and paraganglioma (PGL) belong to the same family of neural crest-derived neoplasms (also called PPGL). PPGLs occur with a frequency of up to 1:500 in patients with hypertension and up to 1:1000 in unselected post-mortem studies [1]. They are widely distributed from the skull base to the pelvis but almost uniquely develop in close relationship with the sympathetic and parasympathetic divisions of the autonomic nervous system. The sympathetic axis includes the adrenal medulla and chromaffin cells located in posterior mediastinum (in the periaortic regions), or the retroperitoneum, while the parasympathetic paraganglia are mainly located in the head and neck region and anterior/middle mediastinum. Based on the classification published in 2004 by the World Health Organization (WHO), the term pheochromocytoma should be reserved solely for adrenal PGL [2]. The term PGL is used to describe extradrenal tumors, regardless of their location (sympathetic or parasympathetic).

Clinical presentation

PHEO accounts for about 4% of adrenal incidentalomas. However, since their prevalence is higher in autopsy series, there is probably underdiagnosis during life. PHEO usually causes symptoms of catecholamine oversecretion (e.g., sustained or paroxysmal elevations in blood pressure, headache, episodic profuse sweating, palpitations, pallor, and apprehension or anxiety). By contrast, head and neck PGLs are often incidentally discovered on imaging studies or are revealed by symptoms and signs of compression or infiltration of adjacent structures (e.g., hearing loss, tinnitus, dysphagia, cranial nerve palsies).

Spectrum of hereditary syndromes

Around 5-10% of solitary PHEOs are hereditary, whereas the presence of multiple PHEOs or the combination of a PHEO with synchronous or metachronous extra-adrenal PGL are related to currently known germline/somatic mutations in more of 70% of cases. These are now recognized to be caused by at least 16 susceptibility genes [3]. Most important correlations between the gene(s) involved and a specific tumor
anatomical predisposition have been found as described below:

1: PHEO: RET, VHL, SDHx, NF1, MAX, TMEM127, and EPAS1/HIF2A.

2: Sympathetic-PGLs: SDHx, VHL, RET, PHD1/2, and EPAS1/HIF2A (somatic mutation).

3: Head and neck PGL (HNPGL): SDHx.

Major predictors for hereditary PPGL include a family history of PPGL, characteristic syndromic presentation, young age at diagnosis, a previous personal history of PPGL, multifocality, unusual location (e.g., heart, urinary bladder), and/or tumor recurrence, particularly in the adrenal gland and a combined elevation of normetanephrine and 3-methoxytyramine [4, 5]. Renal cell carcinoma (RCC), gastrointestinal stromal tumor (GIST), pituitary adenoma and, rarely, pulmonary chondroma, neuroblastoma and neuroendocrine neoplasms (carcinoids) can also be related to SDHx mutations [6-8]. Other manifestations can also be suggestive of certain gene mutations. For example, prior medullary thyroid cancer (MTC) for RET, café-au-lait spots/neurofibromas for NF1, renal cell carcinoma (RCC)/hemangioblastomas/pancreatic tumors for VHL, congenital polycythemia and duodenal somatostatinoma for EPAS1/HIF2A, and RCC/leiomyomas for FH (Table 1).

Furthermore, PPGL with an underlying SDHB mutation are associated with a higher risk of aggressive behavior leading ultimately to death, particularly due to the development of metastatic disease. The risk of malignancy in SDHB mutation-associated tumors has been estimated to range from 31% to 71%. In addition to impacting the distribution of disease, the genomically-distinct subgroups of PPGLs have different patterns of catecholamine secretion and the expression of cell membrane receptors and transporters, which impact their imaging phenotype, particularly the uptake of catecholamines or their precursors [9].

Clinical indications for nuclear imaging

Confirmation of diagnosis of PPGL

The diagnosis of PHEO is often based on the presence of high levels of plasma or urinary metanephrines and methoxytyramine in combination with suspicious characteristic clinical features. Some specific radiologic features of anatomic imaging (CT/MRI) may also be suggestive of the diagnosis [10]. Typically, a PHEO demonstrates avid enhancement but can have a heterogeneous appearance due to cystic, necrotic, or fibrotic regions within the
lesion. In cases of a non-secreting adrenal mass, the high specificity of functional imaging may sometimes contribute to its diagnosis.

In the presence of a retroperitoneal, extra-adrenal non-renal mass, it is important to differentiate a PGL from other tumors or lymph node involvement including metastases. Although specific functional imaging is very helpful to distinguish PGL from other tumors, it is usually not done before biochemical results are available.

In head and neck locations, there are also many differential diagnoses such as lymph node metastasis, neurogenic tumors (e.g. schwannoma, neurofibroma, ganglioneuroma), jugular meningioma, internal jugular vein thrombosis, internal carotid artery aneurysm, hemangioma and vascular malposition.

**Staging at initial presentation of PPGL**

Generally, PPGLs are benign and progress slowly. Metastatic rates vary from less than 1% to more than 70%, depending on tumor location, size, biochemical phenotype and, particularly, genetic background. Functional imaging is probably not necessary in the preoperative work-up of patients meeting the following criteria: >40 yrs, absence of a family history, small (less than 3.0 cm), no multiplicity, adrenergic biochemical phenotype (uniquely pointing towards a tumor in the adrenal gland only) and negative genetic testing. Since the genetic status is often not available before surgery, the presence of multifocal or metastatic disease, substantial locoregional extension, or extremely high methoxytyramine levels calls for nuclear imaging, which is very useful in this regard since it may point towards SDHx mutation. HNPGLs require a specific approach and although metastatic disease is rare, locoregional extension and multifocality are common and often warrant the use of functional imaging modalities as well as detailed anatomical correlation with arterial and venous phase CT or MRI. Early treatment is crucial since most of these tumors become difficult to resect if they are large or involve the skull base.

**Restaging and follow-up**

Nuclear imaging may be used for restaging following completion of treatment of aggressive tumors or as follow-up of non-secretory and asymptomatic lesions. It can also localize occult tumor sites in cases of positive biochemical results, suspicion of disease recurrence or to clarify equivocal findings on anatomic imaging. PPGLs associated with
adverse pathological features, and/or large tumors, elevated methoxytyramine/dopamine and/or the presence of specific germline/somatic mutations should alert a clinician to carry out extended and prolonged (often lifelong) monitoring. In HNPGL, anatomical identification of tumor remnants or recurrences can be difficult after treatment due to postoperative or radiation-induced morphological changes (e.g., fibrosis, edema, necrosis, or presence of surgical material). Conversely, nuclear imaging using specific radiopharmaceuticals is only minimally influenced by the post-treatment sequelae and therefore, enables accurate diagnosis of tumor recurrences that could be missed by structural imaging [11]. Nuclear imaging can also be helpful in assessing responses to therapies in metastatic or in inoperable PPGL.

**Selection for targeted molecular radiotherapy**

Recently, the success of PRRT with $^{177}$Lu-DOTATATE (oxodotreotide) or other $^{90}$Y or $^{177}$Lu radiolabeled somatostatin analogs in patients with inoperable/metastatic GEP NET has given a great impetus toward the use of PRRT for inoperable/metastatic PPGL.

Nuclear imaging (PET or SPECT) gives valuable information when planning targeted radionuclide therapy with radiolabeled $^{[131]}$I]MIBG or PRRT with $^{[177]}$Lu-DOTATATE or other related agents [12]. Besides confirming uptake in lesions, it also helps in personalized dosimetric evaluation of at-risk organs and tumor target.

**Radiotherapy planning**

Nowadays, integration of multi-modality imaging into radiotherapy planning has brought greater precision to the delivery of radiation. Molecular imaging can complement MRI in difficult situations (especially in the evaluation of venous extension from large jugular PGL or tumor recurrences in the surgical bed) and, therefore, could lead to a more accurate definition of biological target volumes, thereby potentially decreasing the likelihood of complications within surrounding normal tissues. This is particularly true for stereotactic radiosurgery, which enables highly elevated biological effective dose delivery to the tumor.

**Useful Clinical information for optimal Imaging and interpretation**

A nuclear medicine physician should obtain the following information whenever possible:
1. Personal history of PPGL and/or other tumors.

2. Personal history of surgery, chemotherapy, and radiotherapy (including timing and frequency).

3. Known genetic mutation or documented family history of PPGL.

4. Results of PPGL-related laboratory tests (metanephrines, methoxytyramine, calcitonin, chromogranin A).

5. Results of previous anatomic and functional imaging modalities (including baseline and nadir on-treatment imaging for the assessment of tumor response(s)).

6. Drugs (e.g. proton pump inhibitors, histamine type-2 receptor antagonists) or conditions (gastric disorders, impaired kidney function, chronic heart failure, hypertension, rheumatoid arthritis, inflammatory bowel disease, non-neuroendocrine neoplasms) that may interfere with the accuracy of procedures and measurements (particularly for chromogranin A).

General considerations for image acquisition and interpretation:

1. PPGL have different preferential sites of origin that must be known. The integration of functional and anatomical imaging on hybrid SPECT/CT or PET/CT devices is strongly preferred.

2. Images are usually acquired from the top of the skull (for a large jugular PGL) to the pelvis. In case of suspicion of recurrent or metastatic disease, whole-body images are needed.

3. Malignancy is defined only by the presence of metastases at sites where chromaffin cells are normally absent (according to current 2017 WHO Classification of Tumours of Endocrine Organs, this includes only bones and lymph nodes).

4. The presence of retroperitoneal PGL or multifocal tumors increases the chance of hereditary syndrome and requires extensive search for additional PPGL and any other syndromic lesions (e.g., most commonly GIST, RCC, pancreatic tumor, hemangioblastoma, medullary thyroid carcinoma, pituitary adenoma, neuroblastoma, somatostatinoma, and/or pancreatic tumor).

5. All non-physiologic and suspicious foci of tracer uptake must be described since PGL may arise in various atypical locations (e.g., orbital, intrathyroidal, hypoglossal, cardiac, pericardial, gallbladder, urinary bladder, liver, cauda equina).
6. Metastases from PPGL are often small and numerous and could be difficult to precisely localize on co-registered CT images of combined SPECT/CT and PET/CT (unenhanced procedure, thick anatomical sections, or positional shift between CT and PET images).

General points to consider while reporting:

1. The clinical setting and the clinical question that is raised.
2. Details of patient preparation, including concomitant drugs that were withheld.
3. The procedure: radiopharmaceutical, activity administered, acquisition protocol, CT parameters in case of hybrid imaging and patient exposure, including the radiopharmaceutical dose and the CT parameters of radiation exposure (volume computed Tomography Dose Index/CTDI\textsubscript{VOL}, Dose-Lengh Product/DLP).
4. The positive findings and interpretation for each anatomical region (i.e., head and neck, chest, abdomen and pelvis, bone/bone marrow).
5. Comparative data analysis with other imaging studies or previous nuclear imaging.
6. Conclusion: The report should present findings in terms of their consistency with a particular diagnosis followed by a listing of study limitations. When conclusive evidence requires additional diagnostic functional or morphologic examinations or an adequate follow-up, this request should be included in the report as could suitability for radionuclide therapy in the case of metastatic disease. Where a hereditary syndrome is suggested, the implications for genetic testing could be raised.
123I-Iobenguane/123I-Metaiodobenzylguanidine scintigraphy

Radiopharmaceutical

MIBG is commercially available labeled with 123I or 131I. [123I]MIBG scintigraphy is highly preferable to [131I]MIBG scintigraphy because (a) it provides higher-quality images (the 159 keV emission of 123I is better adapted to detection with conventional gamma cameras); (b) the lower radiation burden of 123I allows a higher permissible administered activity, resulting in a higher count rate; (c) SPECT can more feasibly be performed with 123I; (d) less time elapses between injection and imaging with [123I]MIBG scintigraphy (24 hours) than with [131I]MIBG scintigraphy (48–72 hours). Nevertheless, [I]MIBG might not be available to every nuclear medicine facility. Although [131I]MIBG can be used in such circumstances, it is not recommended because of low sensitivity and unfavourable dosimetry.

Mechanism of cellular uptake

MIBG, an iodinated analog of guanidine, is structurally similar to NE. Guanidine analogues share the same transport pathway as norepinephrine via the cell membrane NE transporter (NET) system. A non-specific uptake has also been reported for MIBG uptake in PPGL tissues [13, 14]. In the cytoplasmic compartment, MIBG is stored in the neurosecretory granules via vesicular monoamine transporters 1 and 2 (VMAT 1, 2) [15]. MIBG specifically concentrates in tissues expressing catecholamine-secreting tumors, allowing specific detection of other neuroendocrine tumors and, to some degree, in the normal adrenal medulla.

Pharmacokinetics

After IV administration, MIBG concentrates in liver (33%), lungs (3%), heart (0.8%), spleen (0.6%) and salivary glands (0.4%) [16]. In the vascular compartment, the small amount of the remaining MIBG concentrates in platelets through the serotonin (5HT) transporter. Tracer uptake in the normal adrenal glands is weak; the normal adrenals can be faintly visible, especially using [123I]MIBG. The majority of MIBG [16] is excreted unaltered by the kidneys (60-90% of the injected dose is eliminated via urine within 4 days from the day of its administration; 50% within 24h), fecal elimination is minor (<2% up to day 4). In PPGL
patients, uptake in heart and liver is lowered by approximately 40%, most likely as a consequence of competition with circulating catecholamines [17].

Synthesis and quality control

MIBG labeled with $^{123}$I or $^{131}$I is currently commercially available in a “ready to use” formulation that conforms to the European/US Pharmacopeia. The labeled product is available in a sterile solution for intravenous use. The solution is colorless or slightly yellow, contains 0.15-0.5 mg/ml of MIBG, is stable 60 h after synthesis and can be diluted in sterile water or saline. The activity of MIBG should be measured in a calibrated ionization chamber, and radiochemical purity can be evaluated using thin-layer chromatography (TLC).

Drug interactions

Many drugs modify the uptake and storage of MIBG and may interfere with MIBG scintigraphy [18]. It should be underlined that most of the therapeutic pharmaceuticals introduced in the last 25 years and in common use today have never been tested for effect on MIBG uptake [19, 20]. Reported interfering agents include opioids, tricyclic or other antidepressants, sympathomimetics, antipsychotics and antihypertensive agents [21-23]. Labetalol, for example, has been reported to cause false negative scans and should be stopped more than 10 days prior to MIBG administration if a patient’s clinical status allows that [24, 25]. A single oral dose of amitriptyline, a tricyclic antidepressant, significantly enhanced cardiac MIBG washout and compete on the NET with catecholamines resulting in less accumulation of MIBG in PPGL [26]. Post-therapy MIBG scintigraphy failed to detect the vast majority of metastatic PPGL lesions in a polytoxicomanic patient in whom the diagnostic scan was positive [27]. Nifedipine, on the other hand, can cause prolonged retention of MIBG in PPGL [28]. Calcium antagonists are usually listed as medications that interfere with MIBG uptake, but a definitive proof is lacking and probably it is not necessary to withdraw them [19]. Very high serum catecholamines levels may be associated with a lower MIBG accumulation [29-32]. To date, many of these interactions are suspected according to in vitro/preclinical observations or only expected according to their pharmacological properties and thus should be interpreted with caution. Furthermore, mechanisms involved in MIBG uptake or retention may differ between models. For example, specific uptake of MIBG is mediated by 5HT transporters in platelets and by NET in PPGL.
**Side effects**

- Rare adverse events (tachycardia, pallor, vomiting, abdominal pain) can be minimized by slow injection.
- No adverse allergic reactions is expected, although a single case has been reported with $^{[131]}$I-MIBG [33].

**Recommended activity**

$^{[131]}$I-MIBG: 40-80 MBq (adult), $^{[123]}$I-MIBG: 200-400 MBq (adult). Radioactive activity administered to children should be calculated on the basis of a reference dose for an adult, scaled to body weight (for $^{[123]}$I-MIBG: 5.2 MBq/kg with a minimum of 37 MBq and a maximum of 370 MBq for the North American consensus guidelines and a maximum of 400 MBq for the EANM paediatric dosage card); for $^{[123]}$I-MIBG: 35-78 MBq [23].

**Administration**

Intravenous injection. Slow injection is recommended (over at least 1 minute).

**Radiation dosimetry**

The effective dose is 0.013 mSv/MBq for $^{[123]}$I-MIBG and 0.14 mSv/MBq for $^{[131]}$I-MIBG in adult and is 0.037 mSv/MBq for $^{[123]}$I-MIBG and 0.43 mSv/MBq for $^{[131]}$I-MIBG in children (5 years) [34]. There is an increased radiation dose from CT in SPECT/CT protocols, the value being dependent on parameter scan.

**Pregnancy**

The use of radiopharmaceuticals is generally contraindicated in pregnancy. However, if clinically necessary, a decision to perform imaging should be based on the benefits against the possible harm to fetus from the procedure in case of pregnancy, whether known or suspected. Proper institutional and local guidelines should be followed in relation to radiation effects.
Breast feeding

Breast feeding should be discontinued for at least 3 days after scintigraphy using $^{123}$I-MIBG non-contaminated by $^{124}$I or $^{125}$I. Breast feeding should be stopped completely when using $^{131}$I-MIBG.

Renal insufficiency

Reduced plasma clearance of $^{123}$I-MIBG occurs in patients with renal insufficiency and is not cleared by dialysis [35]. Therefore, reduced administered activity by 50% should be considered and possible delayed imaging is recommended.

Patient preparation

- Thyroid blockade (130 mg/day of potassium iodine; equivalent to 100 mg of iodine) started one day before tracer injection and continued 7-10 days for $^{131}$I-MIBG [36], but use of this agent for diagnostic imaging is strongly discouraged. Potassium perchlorate may be substituted for Lugol’s iodine in iodine-allergic patients and started 4 hours before tracer injection and continued for 2 days (400-600 mg/day).
- Discontinuation of drugs interfering with MIBG uptake and retention (as mentioned in prior section). All have to be withheld for 1–3 days, except for labetalol, which should be discontinued 10 days prior, and antipsychotics, for which the withdrawal period should be about 3-4 weeks. Regarding antipsychotic medications, it can be dangerous to stop these medications, despite their potential effects on MIBG uptake. Therefore, this should only be performed based on a very careful consultation with the patient’s psychiatric care team.
- Decision to discontinue other medication should be weighed with the clinical setting and in very good coordination with the managing clinician.

Image acquisition and reconstruction

$^{123}$I-MIBG scans should be obtained approximately 24 hours after tracer injection.

- Imaging parameters
Anterior and posterior planar static images of the head and neck (+ right and left lateral oblique views), thorax, abdomen and pelvis are obtained for 10-15 minutes per image (or about 500 kcounts) (using a 256 × 256 matrix, with a large-field-of-view camera, a low-energy collimator, and with a 20% window centered at the 159 keV photopeak). Whole-body images can be an alternative to planar views and include anterior and posterior acquisitions into 1024 x 512 word or 1024 x 256 word matrix for a minimum of 30 min (speed 6 cm/min max) [37].

Many centers prefer medium energy collimators because they reduce scatter and septal penetration yields of high energy photons that are part of the $^{123}$I decay scheme. However, longer acquisition times required with medium-energy collimators.

SPECT (SPECT/CT) over the anatomical regions showing pathological tracer uptake on planar images often complete the image session and can replace lateral oblique planar images of the head and neck region. The SPECT images are performed for a 360° orbit (128 × 128 word matrix, 6-degree angle steps, 30-45s per stop). Co-registered CT images (100-130kV, mAs modulation recommended) from SPECT/CT cameras enable attenuation and facilitate precise localization of any focus of increased of tracer.

- Reconstruction

Iterative SPECT reconstruction or other validated reconstruction protocols that accurately visualize lesions can be adapted to the clinical setting. CT-based attenuation correction (CTAC) is used for SPECT/CT.

**Imaging interpretation**

- Visual analysis

Physiological distribution: Normal uptake of $[^{123}]$MIBG is observed in myocardium, salivary glands, lacrimal glands, thyroid gland, liver, lungs, adrenal glands (slight uptake can be seen in up to 80% of cases), bowel and uterine uptake during menstrual period. $[^{123}]$MIBG uptake in the adrenal glands is considered normal if mild (less or equal to liver uptake), symmetric and when the glands are not enlarged on CT. Large intestinal activity may also be visible, especially at later imaging times. Brown adipose tissue (BAT) uptake should be considered as a normal distribution of MIBG. Although this may be more common in children compared to
adults, BAT can also be enhanced in the presence of PPGL and can potentially mask head and
neck and adrenal lesions. Beta adrenoceptor blockade can reduce this finding. However, the
use of beta adrenoceptor blockade alone is contraindicated in PPGL patients.

Pathological uptake: As normal adrenal uptake is faint, distinctly increased uptake or
asymmetric adrenal uptake in presence of enlarged gland should be considered to reflect
potential pathology until proven otherwise. Extra-adrenal sites of uptake that are focal and
cannot be explained by normal physiological distribution are considered abnormal.
SPECT/CT is helpful for better localization of abnormal uptake and is generally
recommended

- Quantification
Quantification of uptake is not routinely utilized as the methodology is not fully clinically
established. Quantitative SPECT/CT has been developed to provide dosimetry for therapeutic
radionuclides including $^{177}$Lu [38, 39] but should not be used in routine clinical practice
unless it has been properly validated [40].

Common pitfalls

- False positives
CT-based attenuation correction often leads to enhanced physiological visualization of the
adrenal medulla and may therefore induce false-positive interpretation unless the
interpretation principles detailed above are followed and adapted to allow moderate uptake as
a normal finding. In MEN-2 patients, $[^{123}]$I MIBG scintigraphy is of limited value for
discriminating physiological uptake from diffuse adrenal medullary hyperplasia or PHEO.
False-positive cases have also been related to tracer uptake by other neuroendocrine lesions
(carcinoid tumor, medullary thyroid carcinoma, Merkel cell carcinoma, ganglioneuroma).
Rarely, MIBG uptake has been reported in adrenocortical adenomas or carcinomas,
retroperitoneal angiomyolipomas and hemangiomas. SPECT/CT may avoid misleading
accumulations in the liver (inhomogeneous uptake, hepatic hemangioma, hepatocellular
carcinoma), in the renal parenchyma (diffuse for renal artery stenosis, focal for acute
pyelonephritis) or in the urinary tract (hydronephrosis, renal cysts), atelectasis, pneumonia,
vascular malformations, accessory spleen, adrenal abscess, foregut duplication cysts, hemorrhagic cysts, ovarian torsion, chronic inflammatory foci [23].

- False negatives

HNPGL, SDHx-related PPGLs, small lesions, large PHEO with cystic degeneration, necrosis, or hemorrhage, poorly-differentiated tumors (low expression of VMAT-1) are more prone to yield false-negative results [41-45]. False negative results may also result from interfering medications (drug-interference).

**Diagnostic accuracy**

[\textsuperscript{123}I]MIBG scintigraphy has a sensitivity ranging from 83–100% and a high specificity (95–100%) for PHEO. Studies, which have included high numbers of extra-adrenal, multiple, or hereditary PGLs, found reduced sensitivity of [\textsuperscript{123}I]MIBG scintigraphy (52-75%) [41-44]. [\textsuperscript{123}I]MIBG scintigraphy may be suboptimal in cases with special genotypic features such as SDHB-related PPGLs [45-47]. In patients with metastatic disease, [\textsuperscript{123}I]MIBG scintigraphy may lead to a significant underestimation of the extent of disease with potential to inappropriately guide management. The sensitivity of \textsuperscript{123}I-MIBG scintigraphy is overall low in HNPGLs (from 18 to 50%). However, importantly, [\textsuperscript{123}I]MIBG scintigraphy can be used to select potential candidates for \textsuperscript{131}I-MIBG therapy.

**Indium-111(\textsuperscript{111}In)-Pentetreotide scintigraphy**

**Radiopharmaceutical**

[\textsuperscript{111}In]DTPA-pentetreotide (OctreoScan) is a \textsuperscript{[111In][In(DTPA)]\textsuperscript{0}} conjugate of octreotide, a long-acting somatostatin analog.

**Mechanism of uptake**

[\textsuperscript{111}In]DTPA-pentetreotide specifically binds to somatostatin (SST) receptors expressed on
cell membranes, especially subtypes 2 and 5. SSTR are expressed on many cells of neuroendocrine origin, and therefore tumours derived from those cell types.

**Pharmacokinetics**

$[^{111}\text{In}]^{\text{In}}\text{-DTPA}$-pentetreotide is cleared from the blood, primarily through the kidneys (50% of the injected dose is recovered in the urine by 6 h, 85% within 24 h). Some of the tracer is, however, retained in tubular cells. Hepatobiliary excretion and spleen trapping are respectively 2% and 2.5 % of the administered dose. However, the bowel is often visualized on delayed imaging and the gallbladder can also contain activity and cause diagnostic uncertainty unless carefully correlated with anatomical imaging. Pituitary and thyroid can also be visualized [48, 49].

**Synthesis and quality control**

$[^{111}\text{In}]^{\text{In}}\text{-DTPA}$-pentetreotide is commercially available (Octreoscan®, Covidien) and supplied as a monodose kit for radiolabeling. The kit contains two sterile vials containing lyophilized pentetreotide (10 µg) and $[^{111}\text{In}]$Indium Chloride (122 MBq/1.1mL at ART).

The radiopharmaceutical is prepared by adding the desired activity of $^{111}\text{In}$-chloride into the vial containing pentetreotide at room temperature. The preparation should be used within 6 hours and can be diluted in sterile saline (2-3 mL).

The preparation of the $[^{111}\text{In}]$In-DTPA-pentetreotide is stable for 6 hours, and should not be used if radiochemical purity is less than 98%. The pH of the solution ranges between 3.8 and 4.3.

Thin layer chromatography can be used to check radiochemical purity as follows: solid phase ITLC, mobile-phase 0.1N sodium citrate adjusted with HCl to pH 5, Rf: $^{111}\text{In}$-pentetreotide 0.0, unbound $^{111}\text{In}$ 1.0.

**Drug interactions and side effects**

It has been proposed to temporarily interrupt somatostatin analogue therapy to avoid possible somatostatin receptor blockade, but this is not universally applicable.
Recommended activity

185–222 MBq in adults and ≤ 3 MBq/kg in children [50].

Administration

Slow (1-2 minute) intravenous infusion.

Radiation dosimetry

The effective dose is about 0.054 mSv/MBq in adults and 0.16 mSv/MBq in children (5 years) [51]. There is an increased radiation dose from CT in SPECT/CT protocols, the value being dependent on a parameter scan.

Renal failure

For patients with significant renal failure, high blood pool activity may hamper visualization of uptake foci. After haemodialysis, an interpretable scintigram can be obtained.

Pregnancy

Generally use of radiopharmaceuticals is contraindicated in pregnancy. Clinical decision to use, should consider the benefits against the possible harm of carrying out the procedure in case of pregnancy, whether known or suspected.

Breast feeding

It is not necessary to discontinue breast-feeding after diagnostic use of [111In]In-DTPA-pentetreotide. However, close contact with infants should be restricted during the first 2 days after administration.

Patient preparation

• Somatostatin analogs are rarely used in the treatment of PPGLs. Short-acting somatostatin analogs may be discontinued for 24 h before [111In]In-DTPA-
pentetreotide administration, while long-acting preparations are preferably stopped 4–6 weeks before the study, and patients should be switched to short-acting formulations, if necessary [50, 52].

- Laxatives are advised, especially when the abdomen is the area of interest. It is of note that this is a controversial when SPECT-CT is planned due to less difficulties for avoiding potential pitfalls due to physiological bowel activity.

- To reduce radiation exposure, patients should be well hydrated before and for at least 1 day after injection.

**Image acquisition**

- **Timing of imaging**
  Scans are obtained 4 hours and 24 hours after tracer injection.

- **Imaging field**
  - Acquisitions are performed using two energy peaks at 171 and 245 keV and large-field-of-view medium-energy collimators.
  - Anterior and posterior planar views of the head & neck (+ right and left lateral oblique views) and thorax, abdomen and pelvis are acquired at 4 hours and 24 hours (512 x 512 or 256 x 256 word matrix and are obtained for a 10-15 minutes per view (or about 300 kcounts for the head and neck and 500 kcounts for the rest of the body) [49, 50].
  - Whole-body imaging can be used instead of planar views. For whole-body images: anterior and posterior images are acquired into 1024 x 512 word or 1024 x 256 word matrix for a minimum of 30 min (speed 6 cm/min max).

- SPECT over the anatomical regions showing pathological tracer uptake on planar images are clearly helpful. The SPECT images are performed for a 360° orbit (128 × 128 word matrix, 6-degree angle steps, 30-45s per stop). Co-registered CT images (100-130 kV, mAs modulation recommended) from SPECT/CT cameras enable attenuation and facilitate precise localization of any focus of increased tracer. SPECT/CT images are particularly useful over the abdomen. If only one SPECT acquisition is obtained, acquisition at 24 hour is preferred because of higher target-to-background ratio.
• Optional images
  - Acquisitions (SPECT and/or planar views) may be repeated at 48 hours for clarification of equivocal abdominal findings.

Reconstruction

Iterative SPECT reconstruction or other validated reconstruction protocols that accurately visualize lesions can be adapted to the clinical setting. CT-based attenuation correction (CTAC) for SPECT/CT.

Image analysis

• Visual analysis
  Physiological distribution: Uptake is seen in spleen, kidney, liver, bowel (visible on the 24-hour images), and the gallbladder if fasting. Normal adrenal glands can also be faintly visible.
  Other sites with faint uptake are the pituitary gland and the thyroid (increased diffuse uptake in case of thyroiditis).
  Pathological uptake: Accumulation of radioactivity at an abnormal site is considered to represent somatostatin receptor binding especially if it is present on the scintigrams on the two standard imaging time points.

• Quantification
  The optimal time interval to quantify tumors is at 24 hr post-injection or later. Tumor uptake can be scored according to Krenning as follows: 0 = no uptake; 1 = very low/equivocal uptake; 2 = clear, but faint uptake (less than or equal to liver uptake); 3 = moderate uptake (higher than liver uptake); 4 = intense uptake (equal to or greater than that in the spleen). This scoring is mainly used in selecting candidates for PRRT. A modified Krenning score has also been used for SPECT using the same reference tissues but is not necessarily equivalent, especially for small lesions in the liver that may be Krenning 2 on planar imaging but visible above hepatic parenchyma on SPECT and therefore, modified Krenning score 3.

Pitfalls
• False positives
Renal parapelvic cysts, accessory splenic tissue or abdominal hernia. False positive cases may be related to tracer uptake by other neuroendocrine lesions or other SST2-expressing tumors (thyroid or breast disease are the most frequent causes of false-positives foci) [50]. Since SST2 is overexpressed in activated lymphocytes and macrophages, FP images may also be related to granulomatous and inflammatory diseases.

• False negatives
Small HNPGLs, abdominal PGLs.

Diagnostic accuracy

Considering parasympathetic HNPGLs, several studies have demonstrated the superiority of [111In]In-DTPA-pentetreotide scintigraphy compared to [131I/123I]MIBG scintigraphy, with sensitivities of 89-100% and 18-50%, respectively [53-58]. However, its sensitivity needs to be revised in patients with hereditary syndromes because some additional lesions can be at the millimeter range and not detectable by conventional scintigraphy [59]. The sensitivity of [111In]In-DTPA-pentetreotide is inferior to that of [123I]MIBG scintigraphy in abdominal and metastatic PPGL (except those related to SDHx mutations), even though it can provide additional information in some patients with rapidly progressing metastatic PPGL [41, 60-62]. [111In]In-DTPA-pentetreotide may also detect other syndromic lesions (e.g., neuroendocrine pancreatic tumor, medullary thyroid carcinoma, neuroblastoma, or pituitary tumors). Both single photon agents have been shown to have inferior diagnostic performance compared to the PET/CT techniques described below.

PET imaging with 68Ga-conjugated somatostatin analogs

Radiopharmaceuticals

Imaging somatostatin receptors with PET tracers has been obtained with 3 different DOTA-coupled somatostatin agonists (SSTa), Tyr3-octreotide (DOTATOC, edotreotide), Tyr3-octreotate (DOTATATE, oxodotreotide), and Nal3-octreotide (DOTANOC). All of them are radiolabeled with 68Ga eluate ([68Ga]Ga-SSTa) obtained from 68Ge/68Ga generators eluate.
68Ge/68Ga generators, GalliaPharm® (Eckert Zeigler) and Galli Eo® (IRE ELIT) have received marketing authorization worldwide. DOTATATE and DOTATOC were recently approved by respectively US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

Due to the short half-life of 68Ga (68 min), [68Ga]Ga-SSTa are synthesized exclusively less than 4 h before patient administration on the day of examination. According to each country's regulations, [68Ga]Ga-SSTa manufacturing can either be centralized and the agent be shipped to Nuclear Medicine Departments, or the agent can be synthesized in local radiopharmacies meeting good radiopharmaceutical practices (GMP).

**Mechanism of cellular uptake**

[68Ga]Ga-SSTa target the somatostatin receptor subtype 2 (SST2), which is the most commonly over-expressed receptor in PPGLs, and is internalized into the cells. SST1 is also strongly expressed in some PGLs, while other receptor subtypes are only slightly expressed or are entirely missing. The low expression of SST5 observed in PGLs constitutes a major difference with some endocrine tumors of the gastrointestinal tract. DOTATOC (Tyr3-octreotide), DOTATATE (Tyr3-octreotate), and DOTANOC (Nal3-octreotide) have excellent affinity for SST2 (IC50: 2.5 nM; 0.2 nM; and 1.9 nM respectively). DOTANOC also binds specifically to SST3, SST4 and SST5. DOTATOC also binds to SST5 (although with lower affinity than DOTANOC) [63-65].

Tracer binding and retention depends on density of somatostatin receptors (SSTR) on the cell surface and, the degree of internalization of the ligand/receptor complex. Recently, SSTR antagonists such as [68Ga]Ga-NODAGA-JR11 [66] have been developed, and are still under evaluation. SST antagonists should decrease DOTA-peptide washout and increase target residence time, despite the lack of internalization, as these remain radiopharmaceuticals remain anchored within the cell membrane. 68Ga radiolabeled antagonists can also be applied as a theranostic agents [66].

**Pharmacokinetics**
After IV administration, SSTa concentrate to all SSTR2-expressing organs: pituitary, thyroid, spleen, adrenals, kidney, pancreas, prostate, liver, and salivary glands. There is no uptake in the cerebral cortex or in the heart is reached in 60 to 120 minutes [67]. DOTA peptides showed a bi-exponential blood half-life (2 and 50 min), and are mainly excreted by the kidney (40 to 75% of the injected dose respectively at 3 and 24 h after injection). Less than 2% of the injected dose is excreted in the feces up to 48 h and no radiolabeled metabolites have been reported during the first 4 h.

**Synthesis and quality control**

Currently, two $^{68}$Ge/$^{68}$Ga generators and DOTATOC and DOTATATE have marketing authorization. $^{68}$Ga can be harvested daily through $^{68}$Ge/$^{68}$Ga generators elution for several months. DOTATOC and DOTATATE are available as commercial kits for radiolabeling. Radiolabelling is $^{68}$Ga is robust (radiochemical purity >95%), requires between 20 and 30 minutes, and procedure can be performed manually or by mean of automatic devices.

Briefly, the labeling procedure is divided into different steps and performed using suitable shielding to reduce radiation exposure.

- **$^{68}$Ga chloride elution:** $^{68}$Ge/$^{68}$Ga generators are eluted with hydrochloric acid solution (0.1-1N).

- **DOTA-peptide radiolabeling:** A defined volume of $^{68}$Ga elution chloride and pH adjuster buffer are successively added in aseptic conditions and mixture is heated (95°C, 7-8 min) according to manufacturer recommendations.

- **Purification:** if required based on generator characteristics, a purification step can be performed using an accessory cartridge to reduce the amount of $^{68}$Ge to lower than 0.001%. Radionuclidic identity is then mandatory and tested by half-life measurements, gamma-ray spectral analysis and determination of any long-lived radionuclidic contaminant 24 hours after EOS.

- **Quality controls:** Appearance, pH and radiochemical purity must be assessed before injection using validated methods (i.e., Thin Layer Chromatography or HPLC).
Radiochemical purity of $[^{68}\text{Ga}]\text{Ga-DOTATATE}$ and $[^{68}\text{Ga}]\text{Ga-DOTATOC}$ must be higher than 92% and 95%, respectively. Ongoing routine samples are tested periodically for sterility.

**Drug interactions and side effects**

Somatostatin analogues may affect the tracer accumulation in organ, and in tumour sites [68].

**Recommended activity**

- The activity administered is 2 MBq/kg (100 to 200 MBq).
- The amount of administred SSTa should not exceed 40 mcg.

**Administration**

Slow (1-2 minutes) intravenous infusion.

**Radiation dosimetry**

The effective dose from radiopharmaceutical is approximately 0.021 mSv/MBq in adult [69]. There is an increased radiation dose from CT in SPECT/CT protocols, the value being dependent on a parameter scan.

**Pregnancy**

Clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure in case of pregnancy, whether known or suspected. See $[^{18}\text{F}]\text{F-FDG PET}$ section.

**Breast feeding**

Breast feeding should be discontinued for 12 h after injection.
Patient preparation

No need for fasting before injection. It has been recommended to discontinue octreotide therapy (1 day for short lived molecules and 3-4 weeks for long-acting analogues). To date, this issue is still not definitively clarified.

Image acquisition

Scans are usually obtained from 45 to 90 minutes after tracer injection from base of skull to mid-thighs (or over the whole-body depending on the clinical setting). Although, there is no generally accepted acquisition time in the literature, generally 3 minutes per bed position is adequate. However, acquisition times per bed position should be increased in obese patients, if low activity is available or imaging is delayed beyond 90 minutes to minimize the risk of a low statistical quality scan.

Image reconstruction

Data acquired in the 3D or 2D mode. Iterative reconstruction algorithms represent the current standard for clinical routine. Point spread function algorithms may enhance detection of small lesions but tend to increase apparent intensity of uptake in such structures [70]. This may impact interpretation of uptake in the adrenals. CT-based attenuation correction (CTAC).

Image analysis

• Visual analysis

Physiological distribution: Intense accumulation of radioactivity is seen in the spleen (and accessory splenic tissue if present), kidneys, adrenals, salivary glands and pituitary. Accumulation in the liver is usually less intense than that noted in the spleen. The thyroid can be faintly visible. Additionally, variable tracer uptake is frequently found in the pancreas particularly in the uncinate process due to the high density in pancreatic polypeptide (PP) cells [71]. Prostate gland and breast glandular tissue may show diffuse low-grade uptake of [68Ga]Ga-DOTA-conjugated peptides.
• Quantification

SUV is an easy and useful parameter for tumour characterization, if images are acquired and processed in a standardized manner. It should be ensured that the PET/CT system is calibrated for $^{68}$Ga half-life.

Pitfalls

• False positives

PET could be falsely positive in metastatic lymph nodes due to various cancers, meningiomas, inflammatory processes, pituitary gland, and some rare conditions such as fibrous dysplasia [72, 73]. Focal pancreatic accumulation in the uncinate process may mimic a pancreatic NET.

• False negatives

There has been no sufficient data to draw any firm conclusions. FN findings mainly occur in PHEO. As for other PET radiopharmaceuticals, the urinary bladder may mask intra- or perivesical PGL. Diuretics can be used in selected cases to to circumvent this drawback.

Diagnostic accuracy

The use of $[^{68}\text{Ga}]$Ga-DOTA-SSA in the context of primary PHEOs has been less studied that other PET radiopharmaceuticals, but has shown excellent results in localizing these tumors when they are metastatic or extra-adrenal [73-78]. $[^{68}\text{Ga}]$Ga-DOTA-SSA is more sensitive than $^{123/131}\text{I}$-MIBG scintigraphy. In a recent systematic review and meta-analysis, the pooled detection rate of $[^{68}\text{Ga}]$Ga-DOTA-SSA PET/CT was 93% (95% confidence interval [CI] 91-95%), which was significantly higher than that of $[^{18}\text{F}]$FDOPA ($[^{18}\text{F}]$FDOPA) PET/CT (80% [95% CI 69-88%]), $^{18}$F-FDG PET/CT (74% [95% CI 46-91%]), and $[^{123/131}\text{I}]$I-MIBG scintigraphy (38% [95% CI 20-59%], $P < 0.001$ for all) [79]. Although interesting, this meta-analysis is hampered by mixing PPGLs of various origin, the low number of PHEOs, and the comparison limited to lesion-based analysis.
Head-to-head comparison between $[^{68}\text{Ga}]$Ga-DOTA-SSA and $[^{18}\text{F}]$FDOPA PET/CT has been performed in only 4 studies: one retrospective study from Innsbruck Medical University ($[^{68}\text{Ga}]$Ga-DOTATOC in 20 patients with unknown genetic background) [80], 2 prospective studies from the NIH ($[^{68}\text{Ga}]$Ga-DOTATATE in 17 and 20 patients) [81-83], and one prospective study from La Timone University Hospital ($[^{68}\text{Ga}]$Ga-DOTATATE in 30 patients) [72]. In these studies, $[^{68}\text{Ga}]$Ga-DOTA-SSA PET/CT detected more PPGLs than $^{18}\text{F}$-FDOPA PET/CT, regardless of the genotype [84], as well as compared to $[^{18}\text{F}]$FDG PET/CT in SDHx, metastatic, and head and neck PPGLs. In a recent study from the Royal North Shore Hospital in Australia, $[^{68}\text{Ga}]$Ga-DOTATATE PET/CT had a sensitivity of 84% for PHEO (21/24) and 100% (7/7) for PGL [85]. The elevated clinical value of $[^{68}\text{Ga}]$Ga-DOTA-SSA was also observed in the pediatric population [86]. EPAS1 (HIF2A) mutations remain an exception among susceptibility genes since they lead to PPGLs that concentrate less $[^{68}\text{Ga}]$Ga-labeled-SSA in contrast to SDHx-related PPGLs [87]. This mechanism for this phenotype is currently largely unexplained. Overall, based on these data it is suggestive that $[^{68}\text{Ga}]$Ga-DOTA-SSA PET/CT is the most sensitive tool in the detection of HNPGLs, especially SDHD-related tumors, which may be very small in size and/or fail to sufficiently concentrate $[^{18}\text{F}]$FDOPA. $[^{68}\text{Ga}]$Ga-DOTA-SSA PET/CT might be inferior to $[^{18}\text{F}]$FDOPA PET/CT in the detection PHEOs.

$[^{18}\text{F}]$FDOPA PET

Radiopharmaceutical

L-$[^{18}\text{F}]$6fluoroDOPA

In many countries, $[^{18}\text{F}]$fluorodihydroxyphenylalaniane ($[^{18}\text{F}]$FDOPA) is commercially available as a sterile mono- or multi-dose solution for intravenous use. The solution is colorless or pale yellow. In US, $[^{18}\text{F}]$FDOPA is not approved and, therefore, it is used in the setting of clinical trials (e.g. National Institutes of Health, Maryland).

Mechanism of cellular uptake
PPGL can take-up and decarboxylate amino acids such as DOPA. This property depends on the activity of the L-aromatic amino acid decarboxylase (AADC). DOPA, the precursor of all endogenous catecholamines, is taken up through LAT transporters (mainly LAT1). [$^{18}\text{F}$]FDOPA is converted into [$^{18}\text{F}$]FDA by AADC and is stored in neurosecretory vesicles.

**Pharmacokinetics**

After IV administration, [$^{18}\text{F}$]FDOPA is specifically trapped by neuroendocrine tissue and follows the metabolic pathways of L-DOPA. Plasma [$^{18}\text{F}$]FDOPA is metabolized by COMT and AADC. [$^{18}\text{F}$]FDOPA is quickly converted into [$^{18}\text{F}$]fluorodopamine in the proximal renal tubule and other target tissues and eliminated in the urine (50% within 1 h and the rest within 12 h).

PPGL take up [$^{18}\text{F}$]FDOPA very quickly. Preferably, the acquisition for static clinical PET imaging of PPGL with [$^{18}\text{F}$]FDOPA can start at 20 minutes post-injection for maximum uptake in tumors. Afterward, a very slight decrease of the tumor SUV starts, which still amounts to 80% of the maximum value after 132 minutes [88]. Some authors use premedication with carbidopa (an AADC inhibitor) to improve bioavailability of the tracer and to decrease physiological uptake by the pancreas [89].

**Synthesis and quality control**

Before 2016 [$^{18}\text{F}$]FDOPA was only available through eletrophilic synthesis that requires up to 4 hrs and suffers from low robustness, a low yield of labeling, between 11 and 25% [90, 91] and low stability. Expedited by dilution in an acid solution, eletrophilically produced [$^{18}\text{F}$]FDOPA needs to be extemporaneously neutralized using bicarbonate buffer kit supplied by the manufacturer pH just before the administration. pH determination needs to be performed and should be kept between 4.0 and 5.0.

In 2016, a nucleophilic method was validated and significantly improved the radiolabeling robustness with an increased radiolabeling yield and a ready to use radiopharmaceutical with a stability of 12 hours.

These two formulations seem to be equivalent, and no additional quality control is needed. Striatum uptake of [$^{18}\text{F}$]FDOPA suggests integrity of the labeled molecule and can be used as internal control.
Drug interactions and side effects

Local pain during injection has been reported for $[^{18}\text{F}]$FDOPA produced by electrophilic synthesis (due to acidic pH).

Haloperidol and reserpine have been reported to, respectively, increase and decrease striatal $[^{18}\text{F}]$FDOPA retention [92, 93]. There is no report of drug interaction in PPGLs.

Recommended activity

2-4 Mbq/Kg.

Administration

Intravenous.

Radiation dosimetry

The effective dose in adults is 0.025 mSv/MBq [51]. There is an increased radiation dose from CT in PET/CT protocols, the value being dependent on a parameter scan.

Pregnancy

Clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure in case of pregnancy known or suspected. See $[^{18}\text{F}]$FDG PET section.

Breast feeding

Breast feeding should be discontinued for 12 h after treatment.

Patient preparation
Patients should fast for 3-4 h as other amino acids can competitively inhibit $[^{18}\text{F}]$FDOPA influx. The administration of 200 mg of carbidopa 1 hr prior $[^{18}\text{F}]$FDOPA injection has been reported to increase tumor uptake but its use is not recommended in the setting of PPGL [89].

**Image acquisition**

- Timing of imaging and image fields:
  Scans are usually obtained from 30 to 60 minutes after tracer injection from base of skull to mid-thighs (or over the whole-body depending on the clinical setting).

- Optional images
  - Early acquisition (10 min after tracer injection) centred over the abdomen may be obtained to overcome difficulties in localizing abdominal PGL located near the hepatobiliary system due to physiological tracer elimination.
  - Early acquisition centered over the neck (from 10 to 20 minutes) may also be performed in MEN-2 patients with residual hypercalcitoninemia [94]. Medullary thyroid carcinoma lesions often show rapid washout and are better visualized on these early images [95].

**Image reconstruction**

Data acquired in the 3D or 2D mode. Iterative reconstruction algorithms represent the current standard for clinical routine. CT-based attenuation correction (CTAC).

**Image analysis**

- Visual analysis
  Physiological distribution: the striatum, kidneys, pancreas, liver, gallbladder, biliary tract and duodenum. Adrenal glands can be visible with variable uptake intensity.
  Pathological uptake: any non-physiological extra-adrenal focal uptake or asymmetrical adrenal uptake with concordant enlarged gland or adrenal uptake more intense than liver with concordant enlarged gland.
Quantification

Various PET-derived quantitative indices were found to be correlated with tumor secretion [44].

Pitfalls

- False positives

False positive cases may be related to tracer uptake by other neuroendocrine tumors including prolactinomas [96] or other tumor types in very rare situations [97]. Rarely, uptake may be due to unspecific inflammation (pneumonia, post-operative changes), since high levels of amino acid transport have also been found in macrophages.

- False negatives

$SDHx$-related PPGLs, mainly those arising from the sympathetic paraganglionic system.

Diagnostic accuracy

In a meta-analysis of 11 studies (275 patients), the pooled sensitivity and specificity on a per lesion-based analysis of $[^{18}F]$FDOPA PET/CT in detecting PPGLs were 79% (95% CI 76–81%) and 95% (95% CI 84–99%), respectively [98]. The most significant factors influencing visualization of $[^{18}F]$FDOPA-avid foci are tumor location and genetic status. $[^{18}F]$FDOPA PET/CT is not an MIBG scintigraphy with higher sensitivity but a new specific radiotracer with its own advantages and limitations [44, 47, 99-104].

A special advantage of $[^{18}F]$FDOPA PET/CT over $[^{123}I]$MIBG scintigraphy or other specific PET tracers stem from its limited uptake by normal adrenal glands [105]. This is particularly helpful in hereditary PHEO which can be very small in size (e.g., MAX and RET mutations) [106]. $[^{18}F]$FDOPA PET/CT may also detect residual medullary thyroid carcinoma lesions and other syndromic tumors such as pancreatic neuroendocrine tumors that may occur in VHL patients (especially after carbidopa premedication to decrease the background activity). Several studies show that $[^{18}F]$FDOPA PET/CT is an excellent first-line imaging tool in HNPGLs with a sensitivity >90% [43, 44, 103, 107-111]. This is due to the high avidity of HNPGLs for $[^{18}F]$FDOPA and the absence of physiological uptake in the adjacent structures (excellent signal-to-noise uptake ratio). The specificity of $[^{18}F]$FDOPA is also very
high. Its sensitivity also approaches 100% in sporadic PHEOs, but can be lower in SDHB/D-related PPGLs [43, 44, 59, 98, 103]. In VHL-patients, [18F]FDOPA PET/CT may detect pancreatic neuroendocrine tumors [112]. In metastatic disease, [18F]FDOPA PET/CT demonstrated better performance in SDHB negative patients than in SDHB positive patients (sensitivity 93% in carriers without SDHB mutations vs 20% in patients with SDHB mutations) [44, 100, 103, 113]. Recent studies have shown lower sensitivity compared to [68Ga]Ga-DOTA-SSA in sporadic HNPGLs and metastatic PPGLs. By contrast, [18F]-FDOPA PET/CT is highly sensitive in VHL, EPAS1 (HIF2A), and FH PPGLs [114].

[18F]FDG PET

Radiopharmaceutical

[18F]FDG is commercially available in a “ready to use” formula and conditioned in a sterile mono- or multi-dose solution for intravenous use.

Mechanism of cellular uptake

[18F]FDG is taken up by tumour cells via glucose membrane transporters and phosphorylated by hexokinase into [18F]FDG-6P. [18F]FDG-6P does not follow further enzymatic pathways and accumulates proportionally to the glycolytic cellular rate. It is remarkable that PPGL underlying SDHx mutation are more avid for [18F]FDG than other subtypes. This is mainly due to the accumulation of succinate which could acts as an oncometabolite and both induces metabolic reprogramming (pseudopyoxia) [115-120] and activates surrounding stromal tissue [121, 122]. Other PPGL have variable uptake.

Pharmacokinetics

After IV administration, [18F]FDG is rapidly cleared from the blood, concentrates in brain (8%), heart wall (4%), lung (3%), spleen (0.3%) and liver (5%). There is also high uptake in brain. The majority of the [18F]FDG is excreted unaltered by the kidneys (20% of the injected dose is recovered in the urine within 2 h) [51].
Synthesis and quality control

\[^{18}\text{F}]\text{FDG}\] is commercially available or is prepared «in-house» in a “ready to use” form and conforms to the European and US pharmacopeia.

Drug interactions and side effects

Blood glucose level is measured before administering \[^{18}\text{F}]\text{FDG}\] and thereby should detect any drug interaction on glucose metabolism. Chemotherapy may change \[^{18}\text{F}]\text{FDG}\] tumour uptake by altering cellular metabolism. The timing of restaging with PET depends on the therapy (from 2 to 5 weeks after end of chemotherapy in cases of metastatic tumours).

Recommended activity

2-5 MBq/kg.

Administration

Intravenous

Radiation dosimetry

The effective dose equivalent is 0.019 mSv/MBq [51]. There is an increased radiation dose from CT in PET/CT protocols, the value being dependent on a parameter scan.

Pregnancy

Clinical decision is necessary to consider the benefits against the possible harm of carrying out any procedure in case of pregnancy known or suspected. The International Commission on Radiological Protection (ICRP) reports that for an adult patient the administration of 259 MBq of \[^{18}\text{F}]\text{FDG}\] results in an absorbed radiation dose of 4.7 mGy to the nongravid uterus (i.e. 0.018 mGy/MBq) [123]. Direct measurements of \[^{18}\text{F}]\text{FDG}\] uptake in a case study
suggested somewhat higher doses than are currently provided in standard models [124]. A pregnancy test may help with the decision, provided the 10 day post ovulation blackout is understood. In the event of doubt and in the absence of an emergency, the 10 day rule should be adopted. In Europe, national guidelines may apply.

**Breast feeding**

Breast feeding should be discontinued for 12 h after imaging.

**Patient preparation**

Patients must fast for at least 6 h, prior to $[^{18}F]$FDG injection. PHEO patients with secondary diabetes (about 35% of cases) require specific instructions for glucose control. During $[^{18}F]$FDG injection and the subsequent uptake phase, patients should remain seated or recumbent, kept warm, in a darkened and quiet room. The use of any premedication for reducing brown adipose tissue uptake is contraindicated in the setting of elevated catecholamine levels due to the associated high risk of hypertensive crisis and tachyarrhythmia.

**Image acquisition**

- **Timing of imaging**
  
  Scans are usually obtained at 60 minutes (45 to 90 min) post-injection.

- **Imaging field**
  
  From base of skull to mid-thighs (or whole-body imaging, depending on the clinical setting).

**Image reconstruction**

Data acquired in the 3D or 2D mode. Iterative reconstruction algorithms represent the current standard for clinical routine. CT-based attenuation correction (CTAC).

**Image analysis**
• Visual analysis

Physiological distribution: brain cortex, salivary glands, lymphatic tissue of the Waldeyer’s ring, muscles, brown fat, myocardium, mediastinum, liver, kidneys and bladder, gastrointestinal tract, testis, uterus and ovaries (before menopause). Physiologic $^{18}$F-FDG uptake in BAT occurs predominantly in the younger age group. In patients with PHEO, there is a frequent increase of BAT uptake due to brown adipocyte cell stimulation by norepinephrine. The level of physiological $^{18}$F-FDG uptake in normal adrenal glands is low even after contralateral adrenalectomy for PHEO but contrasts with the enhanced uptake observed after adrenalectomy for cancer of the adrenal cortex [125, 126].

Pathological uptake: any non-physiological extraadrenal focal uptake or adrenal uptake more intense than liver and with concordant enlarged gland.

• Quantification

Various quantitative indices can be described. Highly elevated uptake values are observed in SDHx-related PPGL.

Pitfalls

• False positives

In absence of biochemical information, several potential diagnoses should be considered in cases of highly-avid adrenal masses (especially in the presence of adrenal to liver SUVmax ratio>2): adrenocortical carcinoma (ACC), primary lymphoma, metastasis, myelolipoma (uptake by the myeloid tissue component of the mass) and oncocyteoma [127]. When masses are moderately avid for $^{18}$F-FDG, other etiologies should be considered: adrenal cortex adenoma, ganglioneuroma, metastasis (small lesions or from cancer with lower malignant potential, sarcoma), hematoma and adrenocortical hyperplasia. Extra-adrenal uptake can be due to inflammatory and neoplastic processes.

• False negatives
Non-avid sporadic PHEOs and retroperitoneal extraadrenal PGLs, MEN2-related PHEO, HNPGL.

**Diagnostic accuracy**

$[^{18}F]$FDG PET positivity is a frequent feature of PPGL. Some features are suggestive of PHEO such as well-limited tumor without vena cava involvement, unilateral adrenal involvement, decreased uptake in the central area evidencing parenchymal degeneration (eg., cystic, hematoma) and presence of calcifications on unenhanced CT. Uptake may be widely variable between PHEOs. Sensitivity and NPV are very high (80-100%) but the PPV is lower due to lack of specificity of $[^{18}F]$FDG. $[^{18}F]$FDG PET/CT is mainly influenced by genetic status of patients [125, 128, 129]. In cases of MEN-2 related PHEO, $[^{18}F]$FDG PET/CT is 40% sensitive. $[^{18}F]$FDG PET/CT may also detect other syndromic lesions (e.g., GIST, RCC, pancreatic tumor, medullary thyroid carcinoma, or pituitary tumor) [130]. $[^{18}F]$FDG PET/CT is also more frequently contributive in metastatic disease with SDHB mutations and might be suboptimal in other patients (sensitivity per lesion 83% in SDHB positive vs 62% in SDHB negative cases).

**Other Tracers**

$[^{99m}Tc]$-hydrazinonicotinamide-Tyr(3)-octreotide ($[^{99m}Tc]$Tc-TOC) is increasingly gaining acceptance as a new radiopharmaceutical for diagnosis of somatostatin receptor-expressing tumours [131, 132]. $[^{18}F]$-fluorodopamine ($[^{18}F]$FDA) has been developed at the National Institutes of Health in Bethesda, MD and is currently used as an experimental tracer at the NIH only. $[^{18}F]$FDA is captured by tumor cells via the NE transporter system and stored in intracellular vesicles. $[^{18}F]$FDA PET/CT seems to be a very promising tool in the management of PGLs associated with the sympathetic system [41, 42, 133, 134]. $[^{11}C]$hydroxyephedrine ($[^{11}C]$HED) has also been evaluated, but its synthesis is complex and the short half-life of $[^{11}C]$ is a major drawback for its routine clinical use [135-139]. MIBG analogues for PET imaging have been used in few studies, but to our knowledge, no clinical studies have yet been reported [140-142]. The influence of some new drugs (histone deacetylase inhibitors) on tracer uptake is also subject to investigations [143].
SPECT versus PET imaging protocols

[123]I MIBG and [111]In-pentetreotide scintigraphy are well-established nuclear imaging techniques in the staging and restaging of PPGL. SPECT/CT has now become more widely available and has the advantage of sequential acquisition of both morphological and functional data, thus increasing diagnostic confidence in image interpretation, disease localization together with enhanced sensitivity. However, these conventional techniques are associated with some practical constraints including long imaging times and relatively prolonged uptake times prior to imaging, as well as GI tract artifacts requiring bowel cleansing, thyroid blockage or need for withdrawal of certain medications that can interfere with interpretation. The somewhat low resolution of conventional SPECT imaging might also limit the ability to detect small lesions. Additionally, SPECT does not easily provide a quantifiable estimate of tumour uptake, although this is being increasingly addressed by quantitative SPECT/CT. Thus, the use of PET imaging has been growing rapidly in the imaging of PPGL, paralleled by great efforts towards the development of new highly sensitive tracers with high affinity for cell membrane transporters and receptors. [18F]FDG is the most accessible tracer and plays an important role in the evaluation of SDHx-related PPGL [125, 128]. [18F]FDOPA is also approved in certain countries, but is not FDA-approved in the US. It is, nevertheless, a sensitive tool in evaluating sporadic and perhaps some metastatic PPGLs. Other tracers, such as [18F]FDA or ([11C]meta-hydroxyephedrine ([11C]HED) which are very specific for chromaffin/ganglionic cells but are presently available at only a few centres and not FDA-approved. [11C]HED is limited in use due to the short half-life of 11C. [68Ga]Ga-DOTATATE, which is FDA-approved or [68Ga]Ga-DOTATOC, which is EMA-approved for evaluating GEP NETs, as well as other [68Ga]Ga-conjugated SSTAs are currently used in many centres as first imaging tools for PPGL, regardless of the patient genotype [81, 144] (Table 2).
Recommendations for clinical practice

Successful PPGL management requires an interdisciplinary team approach. Precise identification of clinical context and genetic status of patients enable a personalized use of functional imaging modalities [3, 125, 145-147] (Table 3). It is expected that the early detection of PPGL with modern PET imaging will very soon lead to the best staging of these tumors thus minimizing complications related to mass effect and hormonal excess, facilitating the most appropriate curative treatment options and reducing the risk of metastatic spread.

Apparently sporadic non-metastatic PHEO

$[^{123}\text{I}]$MIBG scintigraphy is less sensitive as $[^{18}\text{F}]$FDOPA PET/CT and superior to $[^{111}\text{In}]$In-pentetreotide in localizing non-metastatic sporadic PHEO. However, $[^{123}\text{I}]$MIBG scintigraphy or $[^{18}\text{F}]$DOPA PET/CT appear sufficient to confirm the diagnosis of large sporadic PHEO even in rare cases of non-hypersecreting PHEO. $[^{18}\text{F}]$FDOPA PET/CT imaging has less practical constraints than $[^{123}\text{I}]$MIBG scintigraphy and has no drug interactions, which can be limiting for PHEO detection. $[^{18}\text{F}]$FDG can provide with genotypic information which is tightly linked to their tumor behavior (i.e., $SDHB$).

HNPGL

$[^{18}\text{F}]$FDOPA and $[^{68}\text{Ga}]$Ga-DOTA-SSAs appear to be the most sensitive PET radiopharmaceuticals in sporadic cases. In $SDHx$-patients, $[^{68}\text{Ga}]$Ga-DOTA-SSA PET/CT can reveal very small tumors, which can be missed by $[^{18}\text{F}]$FDOPA PET/CT. In the absence of $[^{18}\text{F}]$FDOPA or $[^{68}\text{Ga}]$Ga-DOTA-SSA PET/CT, SRS may be used as an alternative approach, considering the limitations given by spatial resolution of SPECT. $[^{18}\text{F}]$FDG PET has high sensitivity in the setting of $SDHx$-related HNPGLs and can complement $[^{18}\text{F}]$FDOPA PET/CT for detecting additional thoracic/abdominal PGLs.

Retroperitoneal extraadrenal non-metastatic PGL
In the case of a retroperitoneal extra-adrenal non-renal mass, imaging should enable differentiation of PGL from neurogenic tumors, lymph node diseases, or mesenchymal tumors. Therefore, the specificity of functional imaging provides an important contribution. Once the diagnosis of PGL has been established, multiplicity of extra-adrenal localizations should be considered. To this purpose, $^{18}$F-FDOPA and $[^{68}\text{Ga}]$Ga-DOTA-SSAs are more specific than $[^{18}\text{F}]$FDG and can show more lesions than $[^{18}\text{F}]$FDG. Therefore, at present, $[^{68}\text{Ga}]$Ga-DOTA-SSA PET/CT is probably the preferred imaging modality, especially in the patients who harbor $SDHx$ mutations.

**Metastatic PPGL**

$[^{18}\text{F}]$FDOPA shows very good results in detecting metastatic lesions in patients with sporadic PPGL. However, its sensitivity decreased in presence of $SDHx$ mutations. $[^{68}\text{Ga}]$DOTA-SSA has shown better results than $[^{18}\text{F}]$FDOPA, regardless of the genetic background and therefore is is becoming the imaging modality of choice for metastatic PPGL. It can also determine if a patient is likely to benefit from PRRT. $[^{18}\text{F}]$FDOPA PET/CT may be the second-line imaging modality in the absence of $SDHB$ mutations, or when genetic status is unknown. $^{18}$F-FDG PET/CT is the second line imaging modality of choice for $SDHB$-related metastatic PPGLs. $[^{123}\text{I}]$MIBG may lead to significant underestimation of metastatic disease with potential to inappropriately guide management. $[^{123}\text{I}]$MIBG and $[^{18}\text{F}]$FDOPA images do not completely overlap. Furthermore, $[^{123}\text{I}]$MIBG is a theranostic radiopharmaceutical and can be used to determine if a patient is eligible for $[^{131}\text{I}]$MIBG therapy. The clinical benefit obtained with high-specific-activity MIBG (Azedra®) in patients with metastatic and/or recurrent and/or unresectable PPGL gives a new impetus toward of MIBG scan for *in vivo* detection of the cell membrane norepinephrine transporter system. This medication has recently received FDA approval. Although not widely available, the PET-equivalent, $[^{124}\text{I}]$MIBG would have significant advantages in terms of spatial resolution and quantitative capability for prospective dosimetry.

**VHL and RET (MEN2)-related PPGL**

Limited data is available from the literature with respect to imaging studies in *VHL* and *RET*
patients. Many of RET patients do not need any specific functional imaging since the tumours are almost always confined to the adrenal gland with very low risk of malignancy. For VHL, nuclear imaging enables detection of adrenal and extra-adrenal PGL. $[^{123}]$MIBG scintigraphy can be used in the detection of these tumours, but sensitivity and specificity are suboptimal. The absence of high $^{18}$F-FDOPA uptake by healthy adrenal glands is an interesting feature in the diagnosis, staging and restaging of VHL/RET-related PHEO. $[^{18}]$FDG PET is also not sufficiently sensitive in this clinical setting. In both disorders, if possible, subtotal adrenalectomy (cortical-sparing surgery) is the treatment of choice [148-150]. Therefore, follow-up should not be delayed beyond the scheduled time for cortical-sparing surgery and $[^{18}]$FDOPA PET/CT together with MRI can help in preoperative mapping PHEO within both adrenals and guide the surgeons towards the most appropriate (feasible) approach.

**Screening of SDHx-mutation carriers**

The transmission of disease is also different across PPGL syndromes. Regarding SDHD and SDHB, although both are autosomal dominant diseases, they have different disease penetrance. Transmission of SDHD-related PPGL is modulated by maternal imprinting (i.e., the disease almost always occurs only when the mutations are inherited from the father). SDHD-related mutations (paternally inherited) have very high overall penetrance (>80%), in contrast to SDHB ones that have an estimated penetrance of only 20-40% [151-154]. A lower SDHD disease penetrance may be observed in studies that included low severity mutations [155].

The optimal follow-up algorithm has not yet been validated in non-proband SDHx-PPGL but most likely requires a more frequent and complete imaging work-up than for their sporadic counterparts. The aim is to detect tumors at early stages of development, thereby minimizing tumor extension and new cranial nerve impairment for SDHD [156], facilitating curative treatment, and potentially reducing the occurrence of metastases, especially in more aggressive genotypes. At initial staging, the use of PET imaging should provide an adequate sensitivity and specificity at whole body scale with limited radiation exposure and very low, if any, risks (2-2.5 mSv for radiopharmaceutical, 1-3 mSv for CT). Based on clinical studies, $[^{68}]$Ga-DOTA-SSAs PET should be prioritized if available over $[^{18}]$FDOPA PET, although its indication has not been specifically studied in this setting non-proband SDHx
cases. In absence of PPGL, follow-up should include annual biochemical screening, and MRI at regular time intervals [157].
### Legends

#### Table 1. Characteristics of the various hereditary PPGL

<table>
<thead>
<tr>
<th></th>
<th>First manifestation</th>
<th>Context at presentation (in index cases)</th>
<th>PHEO at presentation</th>
<th>Additional extra-adrenal PGL</th>
<th>Biochemical phenotype</th>
<th>Malignancy risk</th>
<th>Other tumor types</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MEN2</strong></td>
<td>MTC</td>
<td>Adult</td>
<td>Uni- or bilateral</td>
<td>Very rare</td>
<td>EPI</td>
<td>Very low</td>
<td>Parathyroid adenoma/hyperplasia (MEN-2A)</td>
</tr>
<tr>
<td><strong>NF1</strong></td>
<td>Neurofibromas</td>
<td>Adult</td>
<td>Often unilateral</td>
<td>Very rare</td>
<td>EPI</td>
<td>Very low</td>
<td>Peripheral nerve sheath tumors, optic glioma</td>
</tr>
<tr>
<td><strong>MAX</strong></td>
<td>PHEO</td>
<td>Young adult</td>
<td>Bilateral</td>
<td>Uncommon</td>
<td>EPI and NE</td>
<td>Moderate</td>
<td>Renal oncocytoma</td>
</tr>
<tr>
<td><strong>VHL</strong></td>
<td>PHEO/PGL</td>
<td>Young adult</td>
<td>Uni- or bilateral</td>
<td>Moderate (retroperitoneum)</td>
<td>NE</td>
<td>Low</td>
<td>Multipleb</td>
</tr>
<tr>
<td><strong>SDHA</strong></td>
<td>PHEO/PGL</td>
<td>Adult</td>
<td>Rare</td>
<td>Moderate (retroperitoneum or head and neck)</td>
<td>NE and/or DA</td>
<td>Moderate</td>
<td>GIST, RCC</td>
</tr>
<tr>
<td><strong>SDHB</strong></td>
<td>PHEO/PGL</td>
<td>Adult</td>
<td>Often unilateral</td>
<td>Frequent (retroperitoneum)</td>
<td>NE and/or DA</td>
<td>High</td>
<td>GISTc, pituitary adenoma, RCC</td>
</tr>
<tr>
<td><strong>SDHD</strong></td>
<td>PHEO/PGL</td>
<td>Adult</td>
<td>Uni- or bilateral</td>
<td>Frequent (head and neck)</td>
<td>NE and/or DA</td>
<td>Moderate</td>
<td>GISTc, pituitary adenoma, RCC</td>
</tr>
<tr>
<td>SDHC</td>
<td>PHEO/PGL</td>
<td>Adult Rarely family history of PHEO/PGL</td>
<td>Rare</td>
<td>Frequent (mediastinum)</td>
<td>NE</td>
<td>Low/Moderate</td>
<td>GIST&lt;sup&gt;c&lt;/sup&gt;, RCC</td>
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</tr>
<tr>
<td></td>
<td>HIF2A</td>
<td>polycythemia (often at birth or early in childhood)</td>
<td>Adolescent-young adult females Absence of family history of PPGL</td>
<td>Very rare</td>
<td>Expected (retroperitoneum)</td>
<td>NE</td>
<td>High</td>
</tr>
</tbody>
</table>

<sup>a</sup>NF-1 is characterized by the presence of multiple neurofibromas, café-au-lait spots, Lisch nodules of the iris and other rare disorders.

<sup>b</sup>Non-KIT/PDGFRA gastrointestinal stromal tumors (GISTs) may be caused by mutations in the SDHB, SDHC and SDHD genes and be associated with PGL in the Carney-Stratakis syndrome.

<sup>c</sup>Von Hippel-Lindau disease is an autosomal dominant disorder, which also predisposes to renal tumors and clear cell carcinoma, pancreatic serous cystadenomas, pancreatic neuroendocrine tumours, testicular tumors, hemangioblastoma of the eye and central nervous system.

<sup>d</sup>HIF2A-related PHEOs/PGL are associated with the presence of duodenal somatostatinoma and retinal abnormalities (Pacak-Zhuang syndrome)

EPI: epinephrine, NE: norepinephrine, DA: dopamine.
### Table 2. PPGL radiopharmaceuticals

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Molecular target</th>
<th>Retention</th>
</tr>
</thead>
<tbody>
<tr>
<td>$[^{123}]$I MIBG, $[^{18}]$F FDA or $[^{11}]$C HED</td>
<td>Norepinephrine transporter</td>
<td>Neurosecretory vesicles</td>
</tr>
<tr>
<td>$[^{18}]$F FDOPA</td>
<td>Neutral amino acid transporter System L (LATs)</td>
<td>Decarboxylation (AADC) and retention in neurosecretory vesicles as $[^{18}]$F FDA</td>
</tr>
<tr>
<td>$[^{68}]$Ga Ga-SSA</td>
<td>Somatostatin receptors</td>
<td>Internalization (agonists)</td>
</tr>
<tr>
<td>$[^{18}]$F FDG</td>
<td>Glucose transporters (GLUTs)</td>
<td>Phosphorylation (hexokinase)</td>
</tr>
<tr>
<td></td>
<td>1st-choice</td>
<td>2nd-choice</td>
</tr>
<tr>
<td>------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>PHEO (sporadic)</td>
<td>$[^{18}\text{F}]$FDOPA</td>
<td>$[^{68}\text{Ga}]$Ga-SSA</td>
</tr>
<tr>
<td></td>
<td>or</td>
<td>or $[^{123}\text{I}]$MIBG</td>
</tr>
<tr>
<td>Inherited PHEO (except $SDHx$ : NF1/RET/VHL/MAX)</td>
<td>$[^{18}\text{F}]$FDOPA</td>
<td>$[^{123}\text{I}]$MIBG or $[^{68}\text{Ga}]$Ga-SSA</td>
</tr>
<tr>
<td>HNPGL (sporadic)</td>
<td>$[^{68}\text{Ga}]$Ga-SSA</td>
<td>$[^{18}\text{F}]$FDOPA</td>
</tr>
<tr>
<td>Extraadrenal sympathetic and/or multifocal and/or metastatic and/or $SDHx$ mutation</td>
<td>$[^{68}\text{Ga}]$Ga-SSA</td>
<td>$[^{18}\text{F}]$FDG and $[^{18}\text{F}]$FDOPA</td>
</tr>
</tbody>
</table>

Based on the above considerations, the following algorithm can be proposed based on clinical situations. This algorithm should be adapted to the practical situation in each institution, and should evolve with time.
References


126. Leboulleux S, Deandreis D, Escourrou C, Al Ghuzlan A, Bidault F, Auperin A, et al. Fluorodesoxyglucose uptake in the remaining adrenal glands during the follow-up of patients


