Pheochromocytomas (PHEO) (1–3) are catecholamine-producing tumors that arise from chromaffin cells. PHEO are mostly situated within the adrenal medulla, although in about 9–23% of cases, tumors develop from extraadrenal chromaffin tissue (adjacent to sympathetic ganglia of the neck, mediastinum, abdomen, and pelvis) and are often referred to as paragangliomas (4–6).

PHEO situated in the adrenal gland are identified more commonly than those in extraadrenal tissues, because clinicians usually focus on the adrenal gland as a main source of catecholamine production. Although they usually choose a proper imaging technique to attempt the localization of PHEO in the adrenal gland, they are often confused as to which algorithm to follow and what technique to choose for the detection of extraadrenal PHEO. Furthermore, physicians often neglect the facts that up to approximately 25% of patients with apparent sporadic PHEO may, in fact, be carriers of germline mutations, indicating hereditary disease with a predisposition for extraadrenal, often multifocal, PHEO (7); that in children, multifocal and extraadrenal PHEO are found in up to 30–45% of cases (6, 8–12); that malignant PHEO account for up to 26–35% of cases (13–18); that the prevalence of malignancy in sporadic adrenal PHEO is 9% (5); and that about 10% of patients with PHEO present with metastatic disease at the time of their initial work-up (19). After initial failed surgery, patients with metastatic PHEO are commonly reevaluated using metaiodobenzylguanidine (MIBG) scintigraphy, a modality that should actually be performed before surgery to confirm that a tumor was indeed a PHEO (5–9% of the population harbor an adrenal tumor, most commonly a benign adenoma) (20–22) or to rule out metastatic disease. These patients are then reoperated upon, suffering additional surgery-related complications and substantial financial expenses. Some clinicians consider the presence of sporadic unilateral small PHEO as indicative of benign disease. This was concluded in older studies of series of patients with PHEO (23–25). However, more recent works from large series of patients with benign and malignant disease in the United States and Europe do not support this view; rather, they support the opinion that there are no absolute clinical, imaging, or laboratory criteria to predict malignancy and clinical course of PHEO (5, 16, 19, 26–32). Nevertheless, PHEO tumors with a diameter larger than 5 cm have a higher potential to metastasize, and such patients should be followed more frequently (33). Consequently, it seems that ruling out metastatic PHEO before initial surgery would be useful, because the detection of other lesions may dramatically affect treatment and follow-up.

Localization of PHEO should be attempted using at least two imaging modalities. Anatomical imaging studies [computed tomography (CT) and magnetic resonance imaging (MRI)] should be combined with functional (nuclear medicine) imaging studies for optimal results to locate primary, recurrent, or metastatic PHEO.

Functional imaging studies (enabled by the presence of the noradrenergic transporter system on PHEO cells) include [123I]- or [131I]MIBG scintigraphy, 6-[18F]fluorodopamine ([18F]DA), [18F]dihydroxyphenylalanine ([18F]DOPA), [11C]hydroxyephedrine, and [13]Cepinephrine positron emission tomography (PET) (34–38). Chromaffin cells in various neuroendocrine tissues [such as PHEO, but also medullary thyroid carcinoma (MTC)] express the plasma membrane norepinephrine transporter and the intracellular vesicular monoamine transporter. The norepinephrine transporter is responsible for the cellular uptake of both MIBG (39) and [18F]DA (36). We have recently shown that [18F]DA PET scanning could theoretically represent yet another imaging modality for the detection of MTCs (40) because MTC cells often express the norepinephrine transporter and concentrate MIBG (41).

In most cases, functional imaging modalities are either able to confirm that a tumor is a PHEO or can lead to further diagnostic work-up. For example, in a patient with positive plasma metanephrines and MIBG imaging studies showing uptake in extraadrenal locations, the possible presence of
multiple endocrine neoplasia type 2 (MEN 2)-related tumors (including MTC) should be considered and assessed with measurement of serum calcitonin and/or RET mutations.

Functional imaging studies are also very helpful to rule out metastatic disease in most cases. However, as malignant PHEO may undergo tumor dedifferentiation with loss of specific neurotransmitter transporters (Refs. 42 and 43, and Pacak, K., unpublished observation), leading to the inability to accumulate these isotopes and consequent lack of localization, $[^{18}F]$FDG PET scanning or somatostatin receptor scintigraphy (Octreoscan) may be required as the next step of the imaging algorithm. $[^{18}F]$FDG is a nonspecific imaging agent whose accumulation is based on the higher metabolic rate of tumors compared with surrounding normal tissue. Another characteristic of dedifferentiated tumors is either the loss or the gain of specific receptors. More particularly, malignant PHEO often expresses somatostatin receptors (44–47), thus enabling scintigraphy with the somatostatin analog octreotide.

In this review we provide readers with current views of the roles of various imaging modalities for biochemically proven PHEO based on elevated plasma metanephrines (36, 48–50) with emphasis on new functional PET imaging agents. Furthermore, we recommend an algorithm implementing anatomical and functional imaging modalities to assure proper localization of benign and malignant PHEO. The proposed algorithm serves not only to localize PHEO, but also to confirm that a tumor is indeed a PHEO and to differentiate adrenal tumors, including incidentalomas from PHEO. Whenever possible, in treating benign or malignant PHEO, surgical excision of any accessible mass should be considered (13, 51–54), because it may alleviate symptoms from catecholamine excess, improve quality of life, and possibly in some patients with only osseous metastatic lesions help to increase their survival. However, in the presence of extensive organ metastatic lesions, the removal of primary lesions and incomplete removal of metastatic lesions in organs are not considered to have an effect on the patients’ survival (55), although further studies are needed. The proposed algorithm serves to guide and optimize surgery in patients with adrenal and extraadrenal PHEOs. Finally, although no cost-effectiveness analyses of PHEO localization have yet been performed, we believe that our approach deals with some “cost” issues, including less radiation exposure to patients.

Anatomical imaging

CT and MRI are common initial imaging modalities used for the localization of PHEO. These studies localize PHEO with high sensitivity, but less than optimal specificity. As these imaging modalities are currently less expensive and time consuming as well as more readily available than functional imaging studies, they should be used as first line imaging modalities. In addition, they should always be carried out over the abdomen first, because PHEO are mostly situated within the adrenal medulla. In some specific situations (see below), anatomical imaging for PHEO can be performed with ultrasound (U/S). PHEO that secrete only epinephrine are uncommon, although they are frequently found in patients with MEN 2 (56). Patients with PHEO that secrete only epinephrine have high plasma or urinary epinephrine or metanephrine levels, and almost always have an adrenal tumor. In these patients, CT or MRI of the abdomen are a first choice examination for the diagnostic localization of PHEO. On the other hand, norepinephrine and normetanephrine can be secreted by PHEO localized both within and outside the adrenal gland (48). If no adrenal masses are seen, attention should be focused initially to the paraspinal area (57). The majority of paragangliomas occur in the paraaortic region or around the renal hilum and may be visible on CT/MRI (57).

CT imaging

Adrenal PHEO of 0.5–1.0 cm or larger or metastatic PHEO at least 1.0–2.0 cm in size can be detected by CT (36, 58), preferably with 2- to 5-mm-thick scanning sections (59). As most adrenal PHEO tumors have a diameter of at least 3 cm, they can be readily visualized with CT (Fig. 1A). Adrenal adenomas can be differentiated from metastases with CT densitometry (60–62). More particularly, a homogenous mass with a density measurement of less than 10 Hounsfield units (HU) on an unenhanced CT is most probably an adenoma (62), whereas if the mass is inhomogeneous and/or has a density measurement of 10 HU or more, the diagnosis is uncertain. Although nonfunctioning adenoma is the most common possibility, a metastasis or functioning tumor should also be considered. For cases with inconclusive clinical and biochemical results, further imaging assessment should be sought using washout after administration of contrast medium (61, 63). Small 1- to 2-cm PHEO tumors are usually homogeneous in appearance, with soft tissue density (~40–50 HU) and show uniform enhancement with contrast.
(64). Larger PHEO tumors may undergo hemorrhage and can be inhomogeneous, and areas of low density can be seen after tumor necrosis (57, 64–66).

Extraadrenal PHEO are located close to the inferior vena cava and the abdominal aorta and alongside the sympathetic ganglia and Zuckerkandl’s organ (7–10%), between the inferior mesenteric artery and the aortic bifurcation, in the mediastinum (1%), or near the urinary bladder (1%) (33, 59). Thus, CT of the abdomen and pelvis should be performed first, followed by chest and neck imaging if this CT is negative (33, 66–73). Spiral CT is preferred for small thoracic tumors.

The advantages of CT in the localization of PHEO are the moderate cost and its high sensitivity, which varies between 85–94% if a PHEO is located in the adrenal gland (19, 58, 74, 75). Sensitivity for detecting extraadrenal, metastatic, or recurrent PHEO is about 90% before surgery (58, 76, 77). The sensitivity of CT may decrease to about 77% due to postoperative changes (35, 77). Additionally, the specificity of CT in excluding PHEO has been shown to be limited in some studies, from 29–50% (75, 78, 79). Nevertheless for lesions limited to the adrenal glands, unenhanced CT followed by contrast-enhanced and delayed contrast-enhanced CT imaging yields a sensitivity of 98% and a specificity of 92% (63, 80). CT shows the structures surrounding a PHEO and permits exact localization of the tumor, although in some patients, such as surgical clips, may distort imaging findings (81, 82). In some patients with PHEO, CT may be negative or have equivocal findings, whereas MRI exams are positive (83, 84), but these cases are rare, especially in patients with no history of previous operation. Traditionally, αand possibly also β-adrenergic receptor antagonist administration is advised for patients with biochemically proven PHEO to safely give ionic monomeric iv contrast for enhanced CT examination (64, 85, 86). However, no rise in plasma catecholamines was observed in 10 patients with PHEO who were given ioxel, a nonionic contrast medium, iv (85), so even contrast-enhanced CT does not pose a significant risk of a hypertensive crisis.

If a high quality, unenhanced and delayed enhanced, CTs are performed and the PHEO tumor is localized, there is no need to proceed to MRI, but functional imaging is required to confirm that a tumor is indeed PHEO and to rule out metastatic disease. If the CT is negative, in a patient with biochemically proven PHEO, MRI should be performed. MRI should be substituted for CT in children, pregnant women, and situations where radiation exposure must be minimized (87). Other situations where MRI is needed in addition to/instead of CT are described below.

**MRI imaging**

Another imaging modality that is widely used in the diagnostic work-up of adrenal PHEO or detection of metastatic disease is MRI, with or without gadolinium enhancement (36, 58, 88). On MRI T1 sequences, PHEO have a signal like those of the liver, kidney, and muscle and can be differentiated with ease from adipose tissue. Chemical shift MRI characterizes adrenal masses based on the presence of fat in benign adenomas and the absence of fat in PHEO, metastases, hemorrhagic pseudocysts, or malignant tumors (89–95). The hypervascularity of PHEO makes them appear characteristically bright, with a high signal on T2 sequence (Fig. 1B) and no signal loss on opposed phase images (Fig. 1B) (96). More particularly, almost all PHEO have a more intense signal than that of the liver or muscle and often more intense than fat on T2-weighted images (57, 65, 97). However, such intense signals can be elicited by hemorrhages or hematomas, adenomas, and carcinomas, so an overlap with PHEO must be considered (98–101), and specific additional imaging is needed to confirm that the tumor is PHEO. Atypical PHEO may show medium signal quality on T2-weighted images and an inhomogeneous appearance, especially if they are cystic (102).

Among the advantages of MRI imaging of PHEO are its high sensitivity in detecting adrenal disease (93–100%) (19, 74, 103) and the lack of exposure to ionizing radiation. MRI is a good imaging modality for the detection of intracardiac, juxtacardiac, and juxtavascular PHEO, because it reduces cardiac and respiratory motion-induced artifacts (102), whereas the use of T2 sequences enables better differentiation from surrounding tissues (104). MRI can be carried out with or without using iv contrast agents (which are nevertheless very safe and do not cause the release of catecholamines) (105–107), and thus no preparation with adrenergic blockade is necessary. MRI offers the possibility of multiplanar imaging and superior assessment of the relationship between a tumor and its surrounding vessels (the great vessels in particular) compared with CT, rendering this modality of utmost importance in the evaluation of patients with PHEO in these areas, especially to rule out vessel invasion (75). However, its overall sensitivity for detection of extraadrenal, metastatic, or recurrent PHEO is lower compared with that of adrenal disease (90%) (58, 75, 76, 108). Although some researchers have reported high specificity of MRI in excluding PHEO (100%) (79), in most reports the specificity of this modality has been shown to be limited to about 50% (74, 75). Additionally, MRI is a more expensive imaging modality than CT.

MRI should be used as the initial imaging procedure for imaging PHEO in children or during pregnancy (36, 108, 109), because it does not involve any radiation exposure, or in the case of known allergy to CT contrast agents.

**U/S imaging**

On U/S imaging, PHEO are usually seen as well defined, round or ovoid masses that demonstrate low echogenicity and homogenous consistency (64, 110). Large PHEO tumors frequently undergo hemorrhage or necrosis, and in this case homogeneity is lost (64). The sensitivity of U/S in evaluating PHEO has been assessed in relatively small numbers of patients and has been reported to be 83–89% (87, 111). To the best of our knowledge, extensive studies on the specificity of modern U/S techniques in the diagnosis of PHEO have not been performed, but it is believed to be low, as in older studies where the overall specificity for adrenal tumors was about 60% (112). As U/S is a modality with no radiation exposure, it can be a first-line choice in the diagnostic work-up of PHEO in selected patients, such as pregnant
women (113, 114), infants, and children (34), but it is not superior to MRI. The low cost and ease of using U/S make this imaging modality a sound choice in the initial evaluation of patients suspected of having PHEO in the neck (115). However, 10% of PHEO are cystic, and although they are readily seen with U/S, those located in the adrenal gland must be differentiated from upper pole renal cysts and hepatic cysts (34). Familial/hereditary causes of PHEO (such as MEN 2 syndrome, von Hippel-Lindau disease, or neurofibromatosis type 2) and possibly, in part, referral bias may account for the high prevalence of multifocal (adrenal and extraadrenal) or only extraadrenal PHEO reported in studies of children (diagnosed in up to 30–43% of cases) (6, 8–12). As U/S provides limited views of the abdomen (108), it is inherently insensitive for imaging extraadrenal PHEO and cannot rule out multifocal disease. Similar to CT/MRI, the presence of surgical clips, distorted anatomy, or inadequate preparation of the patient may also render the interpretation of U/S images difficult.

In summary, this modality is not suitable for evaluating adult patients, and we do not recommend it unless under specific conditions (e.g. pregnancy) and in cases where CT and MRI are not available.

Functional imaging

Adrenal masses are present in about 5–9% of the general population (21, 22, 116, 117). Although most adrenal masses are benign, nonfunctional incidentalomas, about 6.5% of incidentally discovered adrenal masses are indeed PHEO (1–3). Thus, most adrenal abnormalities are not PHEO, highlighting the need for specific diagnostic imaging after anatomical studies are performed in patients with suspicion of PHEO. Additionally, as previously stated, there is no consensus on the existence of absolute clinical, imaging, or laboratory criteria to predict malignancy and multiplicity of PHEO (26–28). Thus, in patients diagnosed with PHEO, the need to exclude metastatic disease or multiple tumors is important. This need might be fulfilled with functional imaging modalities using various radiopharmaceuticals that provide physicians with whole body, PHEO-specific, scans. Nuclear medicine imaging is also important in localizing PHEO in patients in whom anatomic imaging is negative and in the detection of metastatic lesions. However, all functional imaging methods are hampered by the excretion of radioisotopes in urine (118–121), thus lowering their ability to localize PHEO close to the kidneys, the head of the pancreas, or the urinary bladder.

PHEO cells usually abundantly express specific catecholamine plasma membrane and vesicular transporter systems, enabling imaging with [131I]- and [123I]MIBG, as well as with several PET ligands (118, 120). In Table 1, we present a list of available radiopharmaceuticals for localization of PHEO. Some are already in clinical use, whereas newer ones are currently undergoing evaluation (122–124).

**TABLE 1. Radiopharmaceuticals used for nuclear medicine imaging studies of PHEO in research and clinical practice (modified in part from Ref. 34)**

<table>
<thead>
<tr>
<th>Uptake mechanism</th>
<th>Ligand</th>
<th>Metabolic activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active transport into neurosecretory granules via noradrenergic transporter system</td>
<td>[123I]MIBG</td>
<td>Norepinephrine analog</td>
</tr>
<tr>
<td></td>
<td>[125I]MIBG</td>
<td>Norepinephrine analog</td>
</tr>
<tr>
<td></td>
<td>[131I]MIBG</td>
<td>Norepinephrine analog</td>
</tr>
<tr>
<td></td>
<td>[76Br]AIBG</td>
<td>Norepinephrine analog</td>
</tr>
<tr>
<td></td>
<td>[11C]Epinephrine</td>
<td>Catecholamine</td>
</tr>
<tr>
<td></td>
<td>[11C]Hydroxyephedrine</td>
<td>Catecholamine analog</td>
</tr>
<tr>
<td></td>
<td>[11C]DOPA</td>
<td>Catecholamine analog</td>
</tr>
<tr>
<td></td>
<td>[11C]Phenylephrine</td>
<td>Catecholamine analog</td>
</tr>
<tr>
<td></td>
<td>[18F]DA</td>
<td>Catecholamine</td>
</tr>
<tr>
<td></td>
<td>[18F]DOPA</td>
<td>Catecholamine precursor</td>
</tr>
<tr>
<td></td>
<td>[11C]Isoproterenol/isoprenaline</td>
<td>Catecholamine analog</td>
</tr>
<tr>
<td>Metabolic intermediate</td>
<td>[123I]Tyr3-octreotide</td>
<td>Glucose analog</td>
</tr>
<tr>
<td></td>
<td>[111In]DOTA-Tyr3-octreotide</td>
<td>Somatostatin analog</td>
</tr>
<tr>
<td></td>
<td>[90Y]DOTA-Tyr3-octreotide</td>
<td>Somatostatin analog</td>
</tr>
<tr>
<td></td>
<td>[90Y]DOTA-Lanreotide</td>
<td>Somatostatin analog</td>
</tr>
<tr>
<td></td>
<td>[111In]DOTA-Lanreotide</td>
<td>Somatostatin analog</td>
</tr>
<tr>
<td></td>
<td>[99mTc]HYNIC-Tyr3-octreotide</td>
<td>Somatostatin analog</td>
</tr>
</tbody>
</table>

DOTA, 1,4,7,10-Tetraazacyclododecane macrocyclic chelator; HYNIC, hydrazinonicotinamide conjugate; AIBG, iodoaminodobenzylguanidine.

* Radiopharmaceutical with therapeutic applications or potential therapeutic applications.

b Positron emitter for PET scanning.
binding to adrenergic receptors and is minimally metabolized. The plasma membrane and vesicular uptake is Na\(^+\) dependent and can be influenced by medications such as certain nasal decongestants, antihypertensives, antidepressants, and antipsychotics, as well as by cocaine (125); all have to be withheld for 1–3 d, depending on the medications, with the exception of depot forms of antipsychotics, for which the withdrawal period suggested is 1 month (125), before undergoing this nuclear medicine examination. Labetalol, in particular, has been shown to significantly reduce \([^{131}\text{I}]\) and \([^{123}\text{I}]\)MIBG uptake (126–128).

\([^{131}\text{I}]\) has a long half-life (8.2 d) and emits high energy \(\gamma\)-radiation (364 keV). For imaging, \([^{131}\text{I}]\)MIBG is administered iv at doses ranging from 0.5–1.0 mCi (18.5–37 MBq) or 0.5 mCi (18.5 MBq)/1.7 m\(^2\), resulting in an absorbed dose of 1 Gy/mCi (129).

\([^{123}\text{I}]\) has a shorter half-life (13 h) and emits lower energy \(\gamma\)-radiation (159 keV) than \([^{131}\text{I}]\). \([^{123}\text{I}]\)MIBG is administered iv at doses ranging from 3 mCi in children to 10 mCi in adults (130). The absorbed radiation dose from 10 mCi (370 MBq) \([^{123}\text{I}]\)MIBG approaches that of 0.5 mCi (18.5 MBq) \([^{131}\text{I}]\)MIBG (131). Currently, however, its availability in the United States is rather limited.

The amount of free \(^{131}\text{I}\) in \([^{131}\text{I}]\)MIBG is less than 5% (132, 133), and after administration, MIBG releases a further small percentage (~3%) of free \(^{131}\text{I}\) (132, 133). To block thyroid accumulation of the free \(^{131}\text{I}\), which may obscure neck paragangliomas and prevent thyroid damage, patients should take a saturated solution of potassium iodide (100 mg twice a day), or in the case of allergy to a saturated solution of potassium iodide, potassium perchlorate should be given (200–300 mg or 15 drops of perchlorate solution twice a day), starting 1 d before the patient receives MIBG, for 4 or 7 d after administration of \([^{123}\text{I}]\)- or \([^{131}\text{I}]\)MIBG, respectively. Despite the use of blockade, a slight risk of decreased thyroid function persists, as seen in experimental conditions with rats (134) and in children who have received larger doses of \([^{131}\text{I}]\)MIBG for therapy of neuroendocrine tumors (135, 136).

Scintigraphy is performed after 24 h and, if necessary, at 48 h for \([^{123}\text{I}]\)MIBG. For \([^{123}\text{I}]\)MIBG, imaging is performed at 24 and 48 h and, if necessary, at 72 h.

Normally, the myocardium, spleen, liver, urinary bladder, lungs, and salivary glands, being rich in sympathetic innervation, show MIBG uptake after 24 h (137–142). On some occasions, the large intestine (143) and the cerebellum (144, 145) may also show MIBG accumulation. Moreover, the normal adrenal medulla may show \([^{123}\text{I}]\)MIBG uptake (in as many as 32–75% of patients after 24 h) (130, 140). The pattern of \([^{123}\text{I}]\)MIBG uptake may be asymmetrical between the left and right adrenals, and caution should be applied in interpreting the images obtained, particularly to avoid unnecessary or misguided surgery. More rarely, \([^{131}\text{I}]\)MIBG uptake is seen in normal adrenal medulla (16% of scans after 48 h) (141). Some of the MIBG is taken up by platelets, and thrombocytopenia may occur (146, 147). Most of the injected MIBG is excreted via the kidneys, with minimal excretion in sweat, saliva, and feces (118, 148).

\([^{131}\text{I}]\) and \([^{123}\text{I}]\)MIBG scintigraphy has been used extensively in the work-up of patients with PHEO (122, 149–152). PHEOs appear as areas of abnormal increased MIBG uptake (Fig. 2A). With \([^{123}\text{I}]\)MIBG, single photon emission CT (SPECT) is usually carried out (153). \([^{123}\text{I}]\)MIBG is particularly useful in detecting recurrent or metastatic PHEO, tumors with fibrosis, or tumors in unusual locations or in areas with distorted anatomy (150, 154, 155).

\([^{131}\text{I}]\)MIBG scintigraphy has a sensitivity ranging from 77–90% and a high specificity (95–100%) for PHEO (151, 152, 156, 157). Likewise, \([^{123}\text{I}]\)MIBG scintigraphy has a sensitivity ranging from 83–100% and a high specificity (95–100%) for PHEO (156, 158). In the clinical setting, for most, but not all, patients, a negative result on \([^{131}\text{I}]\)- or \([^{123}\text{I}]\)MIBG scintigraphy excludes a diagnosis of PHEO, whereas abnormal uptake on \([^{131}\text{I}]\)- or \([^{123}\text{I}]\)MIBG scintigraphy usually confirms the presence of PHEO. Rarely, false positive \([^{131}\text{I}]\)MIBG examinations have been reported in cases of adrenal carcinoma (159) and in infectious lesions such as actinomycosis (160). False negative MIBG examinations may be expected in cases of nonadherence, with instructions to stop medications that

![FIG. 2](image-url) . A. \([^{123}\text{I}]\)MIBG scan of a 63-yr-old patient with a right adrenal PHEO. One focus of uptake is seen (arrow). B. When the same patient was studied with \([^{18}\text{F}]\)DA PET, two foci of uptake were seen (arrows).
interfere with MIBG uptake (125), and with PHEO tumors that have undergone necrosis or dedifferentiated PHEO tumors. Adrenal adenomas have caused false positive \([123I]\)MIBG uptake (161), and anatomical variations of the renal pelvis may also lead to false positive imaging results (162). The higher sensitivities and the option of using SPECT (156, 163–165) lead us to recommend \([123I]\)MIBG over \([131I]\)MIBG scintigraphy wherever possible. Fusion imaging techniques of \([123I]\)MIBG with CT/MRI, although not yet in widespread use, hold great diagnostic potential in the evaluation of patients with PHEO (151).

**PET imaging**

PET imaging is performed within minutes or hours after the injection of short-lived positron-emitting agents. Low radiation exposure and superior spatial resolution are among the advantages of PET, whereas the cost and limited availability of the radiopharmaceuticals and PET equipment (including the radionuclide-producing cyclotron) still prohibit more widespread use. In the evaluation of patients with PHEO, PET with \([18F]\)FDG, \([13C]\)hydroxyephedrine, or \([11C]\)epinephrine have been used most often (37, 166–169). \([18F]\)DOPA is also used, and at the NIH, \([18F]\)DA has been used with success (35, 36).

Increased glucose metabolism characterizes various malignant tumors; thus, the uptake of glucose labeled with \([18F]\)fluoride (half-life, 110 min) can, in theory, be useful in the imaging of these tumors (Fig. 3). In one study of 17 patients, \([18F]\)FDG PET was used with some success for imaging metastatic PHEO and revealed more metastases than \([123I]\)MIBG or \([131I]\)MIBG scans (168). Malignant PHEO may accumulate \([18F]\)FDG more avidly compared with benign PHEO; nevertheless, semiquantitative analysis of standardized uptake values of images obtained with FDG-PET could not distinguish malignant from benign disease (168). Imaging with FDG-PET may be good for localizing dedifferentiated and/or rapidly growing PHEO tumors. Unfortunately, all rapidly metabolizing cells take up glucose, so imaging with \([18F]\)FDG PET remains nonspecific for PHEO and should never be used as an initial study.

In terms of diagnostic localization of PHEO, \([13C]\)hydroxyephedrine and \([11C]\)epinephrine PET have also detected PHEO tumors (37, 166–168). In the most recent study with \([13C]\)hydroxyephedrine PET, radionuclide uptake was seen in eight of 18 patients (37). \([11C]\)Hydroxyephedrine-derived radioactivity appears to decline relatively rapidly from chromaffin cells, possibly because of less efficient vesicular sequestration of this sympathomimetic amine compared with catecholamines. Moreover, epinephrine is a poor substrate for the norepinephrine transporter compared with DA. Among the other shortcomings of \([13C]\)hydroxyephedrine and \([11C]\)epinephrine is the short half-life of \([11C]\)radio- pharmaceuticals (20 min), which renders the implementation of whole body scans difficult. Short half-lives and high costs are also important deterrents to their more widespread availability, as an on-site cyclotron is then needed for production. The same agents that inhibit uptake of MIBG may also inhibit uptake of \([11C]\)methoxyhydroxyephedrine and \([11C]\)epinephrine (168).

\([18F]\)DOPA is a precursor of DA and has also been used in patients with PHEO. Normal adrenals do not show \([18F]\)DOPA uptake. \([18F]\)DOPA was used in a study of 14 patients with benign adrenal PHEO and a small number of patients (n = 3) with extraadrenal, but not metastatic, PHEO (38). In the former group, all tumors were localized with \([18F]\)DOPA PET, whereas in the latter group \([18F]\)DOPA PET imaging was concordant with MRI results in one of three patients and imaged a tumor that was not seen with \([131I]\)MIBG scintigraphy (38). In a recent study of 10 patients with glomus jugulare tumors (which are similar to PHEO, as they arise from the paraganglionic tissue of the head and neck), 11 of the 15 presumed tumors diagnosed by \([18F]\)DOPA PET were confirmed by MRI (170).

DA is a more specific substrate for the norepinephrine transporter compared with most other amines, including norepinephrine or DOPA (171). Consequently, an analog of DA should be a better imaging agent than norepinephrine or DOPA. In view of this, a new sympathoneural imaging agent, \([18F]\)DA, was developed at the NIH. \([18F]\)DA is a positron-emitting analog of DA and a good substrate for both the plasma membrane and intracellular vesicular transporters in catecholamine-synthesizing cells. Administration of \([18F]\)DA results in a tissue-blood concentration ratio of more than 1000 and enables good visualization of these cells (171). Our experience has shown that \([18F]\)DA is an excellent agent to localize adrenal and extraadrenal PHEO, including metastatic lesions (172, 173) (Figs. 2B and 4). We recently published a study of a series of 28 patients with known PHEO in whom \([18F]\)DA PET scans were positive and localized PHEO tumors in all (172). We have also seen patients with negative \([131I]\)MIBG scans, but positive \([18F]\)DA scans, espe-
Somatostatin receptors are recognized. Types 1, 2, and 5 are abundantly expressed in different neuroendocrine tumors, whereas type 4 shows variable expression, and type 3 shows low expression in these tumors (177, 178). Up to 73% of PHEO cells express somatostatin receptors (predominantly types 2 and 4) (47), like other neuroendocrine tumors, as shown by studies using different techniques, such as radioligand binding, immunohistochemistry, in situ hybridization, Northern blotting, ribonuclease protection, and quantitative RT-PCR (179–181). Octreotide is an eight-amino acid-long peptide analog of somatostatin that is metabolically stable and has highest affinity for type 2 somatostatin receptors, high affinity for type 5 receptors, moderate affinity for type 3 receptors, and no affinity for types 1 and 4 receptors of somatostatin (182). [111In]diaminetriaminedipropionic acid (DTPA), with a half-life of 2.8 d and γ-ray emissions of 173 and 247 keV, is usually used for labeling octreotide. Octreotide is internalized through a receptor-mediated process, and conjugation with DTPA (which is a polar molecule) prevents its passage across the lysosomal and other cell membranes (177).

Octreotide is given iv in doses of 3–6 mCi (111–222 MBq), and scintigraphic views are obtained at 4, 24, and 48 h, as needed. SPECT imaging should be performed. Octreotide is predominantly (85%) cleared by the kidneys within 24 h (119, 121). Sites of physiological uptake include mammary glands, liver, spleen, kidneys, bowel gall bladder, pituitary, thyroid, and salivary glands (119–121, 183). Infections, inflammation, and recent surgery cause false positive results (184, 185). Inflamed joints in patients with arthritis also show increased octreotide uptake (34).

Somatostatin receptor scintigraphy (with either [123I]Tyr3-octreotide or [111In]DTPA-octreotide) has been used in patients with PHEO (46, 186–191). However, the interpretation of the Octreoscan is hampered by the normal presence of somatostatin receptors in a wide range of tissues as well as in inflammatory sites. Another drawback to imaging of intraadrenal PHEO with Octreoscan is the significant degree of octreotide uptake seen in the kidneys (192, 193), which reduces the scintigraphic sensitivity of [111In]DTPA-octreotide for small tumors in the perirenal region (192, 193), and although the infusion of amino acid solutions such as lysine and arginine can lower renal uptake, this technique is not yet widely implemented (194). Metastatic PHEO may also show tumor dedifferentiation, resulting in the loss of somatostatin receptors (46, 47), and consequently, negative [111In]DTPA-octreotide studies can also be expected in these patients.

Only a few reports have compared [123I]MIBG/[131I]MIBG with Octreoscan by studying them in the same patients with PHEO (156, 165, 188, 190, 191). Published reports have not found somatostatin receptor scintigraphy to be helpful in the localization of primary PHEO tumors (156), with Octreoscan studies being negative in most patients (66–75%) with benign PHEO (despite positive [123I]MIBG or [131I]MIBG studies) (77, 156). Malignant/metastatic PHEO are better detected with Octreoscan compared with [123I]MIBG (finding 87% vs. 57% of lesions) (156), because MIBG as well as [18F]DA are sometimes negative in patients with malignant PHEO, possibly because of decreased expression of the cell membrane norepinephrine transporter by less well differentiated cells.
(42, 43) (Pacak, K., unpublished observations). In such cases, Octreoscan should be performed to localize PHEO, because this modality has detected lesions in patients with MIBG-negative neuroendocrine tumors (156, 188, 191, 195) (Fig. 5). This is more important, as more metastases of undifferentiated neuroendocrine tumors were positive on Octreoscan compared with metastases of histologically well differentiated neuroendocrine tumors (195).

We currently do not recommend performing PET, MIBG scintigraphy, or Octreoscan as the first imaging modalities in the diagnostic localization of PHEO, because of limited availability compared with CT/MRI and the long waiting time (up to 72 h) for obtaining imaging views, although these modalities are of utility in further diagnostic work-up of PHEO (156, 187).

Proposed imaging algorithm

A generally accepted and cost-effective approach for the diagnostic localization of PHEO has yet to be established. Biochemical confirmation of the disease is crucial (36, 48, 49) and is best achieved by measuring plasma metanephrine and normetanephrine, ensuring, however, adequate withdrawal from medications that interfere with these measurements and lead to false positive results, such as phenoxybenzamine, tricyclic antidepressants, and β-adrenoreceptor blockers (196). Additional biochemical confirmation can be obtained using the clonidine test coupled with measurement of plasma metanephrine and normetanephrine (196, 197). Evaluation aiming to localize PHEOs in the absence of biochemical corroboration is justified only when there is suspicion of familial disease, particularly at a stage before these tumors secrete significant amounts of catecholamines (197).

In Fig. 6, we propose the use of anatomical imaging methods (either CT or MRI) for initial imaging of the adrenals in patients with biochemically proven PHEO. In some cases, such as in children or during pregnancy, MRI is preferred, but ultrasound may also be considered.

As far as CT is concerned, lesions on unenhanced CT with

![Fig. 5. Widespread metastatic disease with lesions in the chest, abdomen, right acetabulum, and right thigh (arrows) seen on an Octreoscan of a 47-yr-old patient with recurrent PHEO. Uptake of octreotide in the right kidney is prominent (asterisk). In this patient, [123I]MIBG studies did not show definite foci of uptake.](image)

**Fig. 6. Algorithm for diagnostic localization of PHEO.** +T1, Positive T1- and T2-weighted MRI examinations; –T2, positive T1- and negative T2-weighted MRI examinations; +, examination positive for tumor; –, examination negative for tumor; *, [123I]MIBG scintigraphy preferred over [131I]MIBG scintigraphy, where available; **, unusual types of PHEOs may not express the norepinephrine transporter system or may have a low number of catecholamine storage granules.
attenuation values lower than 10 HU exclude the presence of PHEO, whereas those with values higher than 10 HU may be followed by contrast-enhanced and delayed enhanced CT examinations (61, 63). If MRI is chosen as the initial anatomical imaging modality, T1 (with chemical shift) and T2 sequences should be performed. Negative CT or MRI imaging of the adrenals, abdomen, and pelvis should be followed by additional CT scans, except where this modality is contra-indicated, such as in children and during pregnancy, where MRI is preferred. If all CT scans are negative, little is to be gained by performing MRI, except in patients with previous surgery that may result in distorted anatomy.

The presence of PHEO should always be ruled out or confirmed with functional imaging (even if CT and MRI are negative, but PHEO is biochemically proven). The functional imaging test of choice is $[^{123}I]MIBG$, or, if this is not available, then $[^{131}I]MIBG$ should be performed. If the MIBG scan is negative, PET studies should be performed with specific ligands, such as somatostatin receptor scintigraphy with Octreoscan or FDG PET, should be carried out. Venous sampling coupled with measurement of catecholamines or, preferably, metanephrines (35, 36, 50) to localize the tumor through the discovery of a secretory gradient is an ultimate modality to be used with caution in selected cases where all imaging methods have failed. This is technically demanding and is best conducted at specialized centers (6, 198–214). If access to such centers is not feasible, then a repeat noninvasive localization work-up after 2–6 months is a more attractive and preferable choice.

Acknowledgments

We thank Clara C. Chen, M.D., for her critical review of the manuscript and her insightful comments; Millie Whately, C.N.M.T., for assistance with preparing this manuscript; and Nikos A. Kourkatsakis, M.D., Ph.D., and Eleni Liapi, M.D., for advice on technical issues.

Received June 25, 2003. Accepted October 31, 2003.

Address all correspondence and requests for reprints to: Karel Pacak, M.D., Ph.D., D.Sc., Unit on Clinical Neuroendocrinology, Pediatric and Reproductive Endocrinology Branch, National Institute of Child Health and Human Development, National Institutes of Health, Building 100, Room 9D42, 10 Center Drive, Bethesda, Maryland 20892. E-mail: karel@mail.nih.gov.

References


Zucker JM 1996 Could somatostatin scintigraphy be superior to MIBG scan in the staging of stage IVs neuroblastoma (Pepper’s syndrome)? Clin Nucl Med 21:930–933


JCEM is published monthly by The Endocrine Society (http://www.endo-society.org), the foremost professional society serving the endocrine community.