Chapter 34 – Pheochromocytoma

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Introduction

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neural crest-derived tumors. PHEOs are chromaffin cell tumors that produce, store, metabolize, and secrete catecholamines [1-3]. The 2004 World Health Organization classification of endocrine tumors defines pheochromocytoma as a tumor arising from catecholamine-producing chromaffin cells in the adrenal medulla, an intra-adrenal PGL. Closely related tumors of extra-adrenal paraganglia are classified as extra-adrenal PGL. While these definitions serve to distinguish the two types of tumor based on location, this does not take into account differences in functional characteristics related to other differences in cellular origin. More specifically, while extra-adrenal PGLs derived from sympathetic nervous system-associated chromaffin tissue almost always produce catecholamines and often lead to hypertension, those derived from parasympathetic tissue (mainly head and neck PGLs) rarely, in less than 20% of cases, produce significant amounts of catecholamines or their metabolites and usually do not cause hypertension; these tumors may be locally invasive but are rarely metastatic. These head and neck PGLs were formerly known as glomus tumor or carotid body tumors. It therefore seems likely that PHEOs will be continued to be defined as catecholamine-producing tumors of intra- and extra-adrenal chromaffin cells, with those derived from the latter types of chromaffin cells classified as extra-adrenal PHEOs. PHEOs typically occur in about 80-85% of cases from adrenal medullary chromaffin tissue and in about 15-20% of cases from extra-adrenal chromaffin tissues [4]. Extra-adrenal PHEOs in the abdomen most commonly arise from a collection of chromaffin tissue around the origin of the inferior mesenteric artery (the organ of Zuckerkandl) or aortic bifurcation [5, 6]. Most PHEOs represent sporadic tumors and about 35% of PHEOs are of familial origin [7]. Sporadic PHEOs are usually unicentric and unilateral while familial PHEOs are often multicentric

and bilateral. Both adrenal and extra-adrenal PGLs display similar histopathological characteristics. Unusual sites in the abdomen and pelvis include kidney, bladder, urethra, prostate, spermatic cord, genital tract, and liver. About 4-10% of patients with PHEO present with adrenal incidentaloma, whereas approximately 5% are diagnosed at surgery [8-10]. Although metastases may be rare for adrenal (about 10%) and familial (less than 5%) PHEOs [11], the prevalence is up to 36-50% for extra-adrenal abdominal PHEOs or even higher in those with succinate dehydrogenase subunit B gene mutation [12-15]. Finally, up to 10% of intra-adrenal PHEOs recur locally [16, 17]. PHEOs occur in about 0.05% to 0.1% of patients with sustained hypertension. However, this probably accounts for only 50% of persons harboring PHEO, when it is considered that about half the patients with PHEO have only paroxysmal hypertension or are normotensive. Also, it must also be considered that the prevalence of sustained hypertension in the adult population of Western countries is between 15 to 20% [1, 5, 18]. Thus, in Western countries the prevalence of PHEO can be estimated at 1:2,500 to 1:6,500 patients, with an annual incidence in the United States of 500 to 1,100 cases per year. Despite this low incidence, PHEO must always be considered because if identified, it can be cured in about 90% cases, whereas left untreated, the tumor is likely to be fatal due catecholamine-induced malignant hypertension, heart failure, myocardial infarction, stroke, ventricular arrhythmias, or metastatic disease.

Clinical Presentation

Although the presence of signs and symptoms of catecholamine excess remains the principal reason for initial suspicion of PHEO, this does not imply that all PHEOs exhibit such manifestations. Increasing proportions of these tumors are now being discovered incidentally during imaging procedures for unrelated conditions or during routine periodic screening in patients with identified mutations that predispose to the tumor. In such patients the clinical presentation may differ considerably from those in whom the tumor is suspected based on signs and symptoms.

The varied signs and symptoms of PHEO mainly reflect the hemodynamic and metabolic actions of the catecholamines produced and secreted by the tumors [19]. However if testing of the VHL gene is consider in a patient with PGL, and no familial or clinical evidence of VHL syndrome the tumors are characterized by production of normetanephrine (rarely with methoxytyramine) and without production of metanephrine [20, 21]. Hypertension is the most common sign and may be sustained or paroxysmal,

with the latter more usual presentation occurring on a background of normotension or sustained hypertension. PHEO may also present with hypotension, particularly postural hypotension or alternating episodes of high and low blood pressure [22]

Table 1. Clinical symptoms and signs characteristic of patients presenting with pheochromocytoma

Symptoms	Percent
Headache	70-90
Palpitations ± tachycardia	50-70
Diaphoresis	60-70
Anxiety	20
Nervousness	35-40
Abdominal/chest pain	20-50
Nausea	26-43
Fatigue	15-40
Dyspnea	11-19
Dizziness	3-11
Heat intolerance	13-15
Pain/Paresthesias	up to 11
Visual symptoms	3-21
Constipation	10
Diarrhea	6
Hypertension	>98
(Hypertension) sustained	50-60
(Hypertension) paroxysmal	50
Orthostatic hypotension	12
Pallor	30-60
Flushing	18

Table 1. Clinical symptoms and signs characteristic of patients presenting with pheochromocytoma	
Symptoms	**Percent**
Fever	up to 66
Hyperglycemia	42
Vomiting	26-43
Convulsions	3-5
Adapted from Ram and Fierro-Carrion [18], Manger and Gifford [5] and Werbel and Ober [29]	

As illustrated in Table 1, symptoms of PHEO are wide ranging and, in isolation, not uncommon in the general population. Headache occurs in up to 90% of patients with PHEO [1, 23-27]. In some patients catecholamine-induced headache may be similar to tension headache. Excessive, most commonly, truncal sweating occurs in approximately 60-70% patients. A typical sign of catecholamine excess is also pallor seen in approximately 27% of patients whereas flushing is much less common. The presence of triad including headache, palpitations and generalized inappropriate sweating in patients with hypertension arouse immediate suspicion for a PHEO. Other common complaints are severe anxiety, tremulousness, nausea, vomiting, weakness, fatigue, dyspnea, weight loss despite normal appetite (caused by catecholamine-induced glycogenolysis and lipolysis), visual problems during an attack and profound tiredness and polyuria most commonly experienced after an attack. Most patients also present with severe episodes of anxiety, nervousness, or panic attacks. Less frequent clinical manifestations include fever of unknown origin (hypermetabolic state) and constipation [26-28]. Except for clinical signs and symptoms as described above, patients with malignant PHEO can, in up to 54% of cases, present with tumor related pain due to large primary tumors or due to metastatic lesions, most often bone metastases [29].

Attacks (spells) of signs and symptoms may occur weekly, several times daily, or as infrequently as once every few months. Most last less than an hour, but rarely more than several days. Attacks may be precipitated by palpitation of the tumor, postural changes, exertion, anxiety, trauma, pain, ingestion of foods or beverages containing tyramine (certain cheeses, beers, and wines), use of certain drugs (histamine, glucagon, tyramine, phenothiazine, metoclopramide, adrenocorticotropic hormone), intubation,

induction of anesthesia, chemotherapy, endoscopy, catheterization, and micturition or bladder distention (with bladder tumors) [30].

Highly variable symptomatology in patients with PHEO may reflect variations in nature and types of catecholamines secreted, as well as co-secretion of neuropeptides: vasoactive intestinal peptide, corticotrophin, neuropeptide Y, atrial natriuretic factor, growth hormone-releasing factor; somatostatin, parathyroid hormone-related peptide, calcitonin, and adrenomedulin. The classic example is the PHEO with ectopic secretion of corticotrophin or corticotrophin-releasing factor, resulting in the presentation of Cushing's syndrome. PHEOs have also been described that secrete excessive amounts of vasoactive intestinal peptide, this resulting in presentation of watery diarrhea and hypokalemia.

Differential Diagnosis

Since the clinical presentation of PHEO and PGL can be highly variable, with similar signs and symptoms produced by numerous other clinical conditions (Table 2), the tumor is often referred to as the "great mimic". As discussed in detail elsewhere, distinguishing PHEO from these and other less common conditions can be a challenge to the diagnostic acumen of any clinician.

Table 2. Differential diagnosis of pheochromocytoma

Endocrine	1. adrenal medullary hyperplasia 2. hyperthyroidism, thyroid storm 3. carcinoid 4. hypoglycemia (often due to the presence of insulinoma) 5. medullary thyroid carcinoma 6. mastocytosis 7. menopausal syndrome
Cardiovascular	1. heart failure 2. arrhythmias 3. ischemic heart disease, angina pectoris 4. baroreflex failure a. syncope

	b. orthostatic hypertension c. labile hypernoradrenergic essential hypertension d. renovascular disease
Neurologic	1. migraine or cluster headaches 2. stroke 3. diencephalic autonomic epilepsy 4. meningioma a. POTS (postural orthostatic tachycardia syndrome) b. Guillain-Barre syndrom c. encephalitis
Psychogenic	1. anxiety or panic attacks a. factitious use of drugs b. somatization disorder c. hyperventilation
Pharmacologic	1. tricyclic antidepressant a. cocaine b. alcohol withdrawal c. drugs stimulating adrenergic receptors d. abrupt clonidine withdrawal e. dopamine antagonists f. monoamine oxidase inhibitors g. ephedrine-containing drugs h. factitious use of various drugs including catecholamines
Miscellaneous	1. neuroblastoma, ganglioneuroma, ganglioneuroblastoma 2. actute intermittent porphyria a. mastocytosis b. unexplained flushing spells c. recurrent idiopathic anaphylaxis d. lead and mercury poisoning

Adapted from Lenders et al [1]

To first think of the tumor therefore remains the critical first step for diagnosis. Nevertheless, as a dangerous yet mostly curable cause of secondary hypertension, the high prevalence of hypertension in the general population also means that these tumors are frequently searched for, but rarely found. Most patients tested for PHEO or PGL do not have the tumor and it remains important to consider other underlying clinical conditions.

Resistance to various antihypertensive medications or paroxysmal blood pressure increases during treatment with β-blockers, or associated with conditions known to precipitate attacks (mentioned above), should suggest PHEO. It is also important to recognize that many other conditions, such as obstructive sleep apnea, may result in resistant or paroxysmal hypertension, with headaches and other symptoms. In obstructive sleep apnea there is also sympathetic activation, which may lead to increases in urinary outputs and plasma levels of catecholamines, further complicating differential diagnosis.

Paroxysmal hypertension represents a frequent clinical dilemma, particularly when these bouts are of abrupt onset and severe (blood pressure > 200/110). Although severe paroxysmal hypertension should always arouse suspicions of PHEO, it can also reflect clinical entity called pseudopheochromocytoma. Pseudopheochromocytoma refers to the large majority of individuals (most often women) with severe paroxysmal hypertension, whether normotensive or hypertensive between episodes, in whom PHEO has been ruled out [31,32]. Recent evidence indicated that pseudopheochromocytoma is a heterogeneous clinical condition subdivided into a primary and a secondary form. In contrast to a primary form, a secondary form is associated with various pathologies (e.g. hypoglycemia, epilepsy, and baroreceptor failure), medications, or drug abuse. The most common clinical characteristics of this syndrome might be in many cases attributable to a short-term activation of the sympathetic nervous system. Paroxysmal hypertension is usually associated with tachycardia, palpitations, nervousness, tremor, weakness, excessive sweating, and pounding headache, feeling hot, facial paleness or rarely redness. In contrast to PHEO, patients with pseudopheochromocytoma more often present with panic attacks or anxiety, flushing, nausea, and polyuria. Another important feature distinctive from PHEO are the circumstances under which episode occur. In PHEO, symptoms are usually unprovoked, while in pseudopheochromocytoma they

usually follow some identifiable events. It is important, therefore, in questioning these patients, to search for specific provocative factors that may have precipitated these episodes. Similar to PHEO, episodes may last from few minutes to several hours and may occur daily or once every few months. Between episodes blood pressure is normal or may be mildly elevated. Pseudopheochromocytoma is usually successfully treatable by antihypertensive drugs or psychotherapy.

It is extremely important to appreciate that congestive heart failure may be caused by catecholamine myocarditis and cardiomyopathy secondary to PHEO. Prompt recognition is crucial since appropriate treatment may return even severely depressed cardiac function to normal, avoiding unnecessary heart transplant.

End stage renal failure is a condition often associated with significant hemodynamic instability, with episodes of hypertension. Numerous cases of PHEO have been described in patients with renal insufficiency, including some in whom the tumor contributed to impaired kidney function, which attests to the importance of differential diagnosis in such patients.

PHEO should also be considered in unexplained shock, especially if accompanied by abdominal pain, pulmonary edema, and pronounced mydriasis unreactive to light. Another rare presentation is multi-system organ failure accompanied by severe hypertension or hypotension, encephalopathy, hyperpyrexia, and lactic acidosis (i.e., PHEO multi-system crisis). However, only rarely will prompt recognition and immediate intervention reverse these conditions, which are usually lethal.

Several neurological disorders may mimic a PHEO, the most well-known being migraine or cluster headaches. Less commonly, stroke, epilepsy or cerebral tumors may arouse diagnostic confusion. Symptoms of stroke or seizures may also occur as the presenting manifestation of a PHEO. Diencephalic autonomic epilepsy represents another neurological condition causing paroxysms of hypertension and tachycardia — sometimes with flushing, diaphoresis and other autonomic disturbances — that may masquerade as PHEO.

Baroreflex failure, characterized by volatile hypertension and hypotension, with tachycardia, can closely resemble PHEO. The condition often presents with hypertensive crises with symptoms of diaphoresis and headache. Some patients may present with substantial elevations of plasma or urinary norepinephrine. The underlying pathology in baroreflex failure can usually, however, be traced to denervation of carotid baroreceptors following carotid body tumour resection, carotid artery surgery, neck irradiation or neck trauma.

Systemic mastocytosis (mast cell disease) and carcinoid syndrome are two conditions with manifestations that sometimes mimic those of PHEO The most frequent symptom in both conditions is flushing and hemodynamic instability, mainly involving hypotension, but also occasionally hypertension. Patients with systemic mastocytosis may also present with postural tachycardia syndrome associated with flushing episodes.

Many of the above conditions can be excluded clinically, but excluding PHEO usually requires biochemical testing. For this, it always important to recognize that some of the above clinical conditions and many types of stress (e.g., strenuous exercise, myocardial infarction, congestive heart failure, hypoglycemia, increased intracranial pressure, hypoxia, acidosis, surgery, trauma) will elevate plasma and urinary catecholamines and their metabolites, making diagnosis difficult.

Genetics

Advances in genetics and recognition of a high prevalence of PHEO in certain familial syndromes is now making it mandatory for routine screening of the tumor in patients with identified mutations, even in the absence of normally considered clinical signs and symptoms. Accumulating data also indicates that many more PHEOs are due to germ-line mutations than previously recognized, raising the importance of considering an underlying hereditary condition even when there is no obvious familial condition. According to the recent publications, up to 30-40% of these tumors are genetically inherited [33,34]

Now, the group of susceptibility genes includes the following genes: the von Hippel–Lindau (VHL) tumor suppressor gene leading to VHL syndrome, the rearranged during transfection (RET) protooncogene leading to multiple endocrine neoplasia type 2, the neurofibromatosis type 1 (NF1) tumor suppressor gene associated with von Recklinghausen's disease, genes encoding the four subunits (A, B, C, and D) of the succinate dehydrogenase (SDH) complex associated with familial paragangliomas and pheochromocytomas known as hereditary paraganglioma (PGL) syndromes (PGL4, PGL3 and PGL1 respectively), and a gene encoding the enzyme responsible for flavination of the SDHA subunit (SDHAF2 was noted to be mutated in a family with hereditary paragangliomas [35]. In addition to these PHEO/PGL susceptibility genes, two other genes, KIF1β an d PHD2, have also been associated with PHEO/PGL development, however very rarely. Recently, three other genes, TMEM127, MYC-

associated factor X (MAX), and hypoxia-inducible factor 2α (HIF2A) (both somatic and germline mutations found), have been described [34, 36, 37, 38]

Somatic mutations in the known PHEO/PGL susceptibility genes have been reported a rare event, but recently, Burnichon et al [37] detected somatic mutations of the RET and VHL genes in about 14% of sporadic PHEOs/PGLs. Furthermore, Welander et al [39] suggested that the NF1 gene constitutes the most frequent (24%) target of somatic mutations so far known in sporadic PHEOs. Recently, it is been identified germline mutations in a new tumor susceptibility gene, MAX, and were found to be responsible of 1.65% in patients with PHEO/PGL without evidence of other known mutations. [37]. Thus, the proportion of all patients with PHEOs/PGLs because of the gene mutations described above is estimated to be approximately 50% at present (Table 3).

Mutation testing, now routinely available for four of the above genes (RET, VHL, SDHB, and SDHD), demonstrates that germline mutations are responsible for about 30 to 40% of all PHEOs, well in excess of the 10% of tumors previously thought to be hereditary [4, 40]. Most importantly, between 12-24% of tumors with no obvious syndrome or family history appear to be due to otherwise unsuspected germline mutations in one of the above four genes. It has, therefore, been suggested that mutation testing should be considered in all patients with PHEO, independently of the presence of any obvious syndrome or family history. In a recent Italian review 82% of germline mutations were detected in patients under the age of 50 [41].

Approximately 50% of patients with MEN 2A or 2B develop PHEO, usually following the manifestation of medullary thyroid cancer, which has a higher penetrance. PHEOs in MEN 2A are most often diagnosed between 30-40 years of age are almost exclusively benign (with less than 5% reported to be malignant) and localized to the adrenals [42]. The risk for development of PHEO is the highest in codon 634 mutation [43, 44]. In MEN 2B germline *ret* mutations represented by a single methionine to threonine substitution at codon 918 in exon 16 of *ret*, the tyrosine kinase domain, is associated with the development of PHEO [45-47]. About one third are bilateral at diagnosis, and about 50% of patients with unilateral disease, develop a second PHEO in the contralateral adrenal within 10 years. Prognosis is good after surgical resection. Due to the rarity of the condition, there are no adequate data to reliably assess survival of MEN 2 patients with malignant PHEO. In children with MEN 2B-associated PHEOs, a higher risk of malignancy compared to MEN 2A or sporadic disease is found.

Table 3. Genotype-phenotype correlations in pheochromocytoma/paraganglioma because of mutation in susceptibility genes

Gene	Locus	Syndrome	Inh	Malignant PHEO/PGL	Single PHEO	Bilateral PHEO	TAPGL	HNPGL	Multiple PGL	Biochemical phenotype
SDHA	5p15		AD	?	-	-	+	+	-	?
SDHB	1p 36.13	PGL4	AD	+++	++	+	+++	++	++	MT, NMN, MTY or NS
SDHC	1q 21	PGL3	AD	±	±	-	+	++	+	MT, NMN or NS
SDHD	11q 23	PGL1	AD PI	+	+	+	++	+++	+++	MT, NMN, MTY or NS
SDHAF2	11q 13.1	PGL2	AD PI	?	-	-	-	+++	++	?
VHL	3p25-p26	VHL	AD	+	++	+++	+	±	+	NMN
NF1	17q 11.2	NF1	AD	+	+	±	-	-	-	MN, NMN
RET	10q 11.2	MEN2	AD	±	++	++	-	-	-	MN, NMN
MAX	14q 23.3	Not known	AD PI	+	++	++	-	-	-	Mixed: NMN, MN
TMEM127	2q 11.2	Not known	AD	±	+++	++	±	±	±	MN NMN
HIF2A	2p 21p16	Yes	Somatic (1 case - germline)	?	±	+	++	-	+++	NMN
KIF1β		Not known	Somatic	?	+	+	-	-	-	?
PHD2	1q42.1	Yes	Germline	?	-	-	+	-	-	?

AD, autosomal dominant; HNPGL, head and neck paraganglioma; Inh, inheritance; MN, metanephrine; MTY, methoxytyramine; NMN, normetanephrine; NS,nonsecreting; PGL, paraganglioma; PHEO, heochromocytoma; PI, paternal inheritance; TAPGL, thoracic or abdominal paraganglioma; ?, unknown.
SDHx-related paragangliomas can be also associated with SDH-deficient gastrointestinal stromal tumors (GISTs). This autosomal-dominant familial paraganglioma and GIST syndrome is known as Carney–Stratakis syndrome. Recently, Pacak–Zhuang syndrome including multiple paragangliomas, somatostatinomas, and polycythemia in females has been introduced. This syndrome is associated with somatic *HIF2A* gain-of-function mutation.

On average about 10 to 20% of patients with VHL disease develop PHEO, but this incidence varies dramatically from family to family depending on the specific mutation [48-51]. The mean age at diagnosis is 28 years, and in about 50% of cases PHEOs are bilateral. Most VHL mutations associated with PHEO also predispose to renal cell carcinoma [52].

Although neurofibromatosis type 1 as an autosomal dominant disorder is the most common familial cancer syndrome predisposing to PHEO, the risk of PHEO in this disorder is about 1% [53, 54]. PHEOs in patients with neurofibromatosis type 1 occur at the fifth decade.

Mutations of genes encoding SDHB, SDHD, SDH5 and rarely SDHC are the most recently identified genetic causes of PGLs [55-58]. Mutations of these genes are associated with relatively high rates of extra-adrenal compared to adrenal tumors, but SDHB mutations appear to be associated with more aggressive tumor behavior and a higher rate of malignancy [59-64]. In several separate studies, malignant disease was found in 38% to 83% of patients with tumors associated with germline SDHB mutations [59-61, 64]. These are much higher rates compared with catecholamine-producing tumors due to other mutations or in patients with sporadic extra-adrenal PGL where rates of malignancy are less than 10%. Malignancy is defined as the presence of metastatic lesions at sites where chromaffin tissue is normally absent (lymph nodes, bone, lung and liver). See Table 3 for summary of genetic inheritable causes of PHEO.

It should be noted that mediastinal PGLs although rare accounting for only 2% of all PGLs, have been associated with mutations in succinate dehydrogenase genes. Sixty percent of patients with primary mediastinal PGL had documented metastatic disease. Due to this data, it is recommended that all patients with mediastinal PGLs be assessed for SDHx gene mutations regardless of age [65].

At the First International Symposium on Pheochromocytoma held in Bethesda, USA a panel of experts convened to outline recommendations for genetic testing agreed that there is now a reasonable argument for more widespread genetic testing than would have been previously considered. It is neither appropriate nor currently cost-effective to test every disease-causing gene in every patient with a PHEO. Rather, it was stressed that the decision to test and which genes to test requires judicious consideration of numerous factors. The importance of a complete clinical work-up and a specialized genetic consultation to collect family history, outline potential repercussions of genetic testing, and obtain appropriate informed consent was outlined as of paramount importance to any decision about genetic testing. Since hereditary tumors usually occur at a younger age than sporadic tumors, age at presentation was also outlined as an important consideration for the likelihood of an underlying mutation. A hereditary basis is particularly important to consider in children with PHEO. Recent papers suggested that patients younger than 50 years old should undergo genetic testing [4, 40, 65].

Apart from the obvious clinical manifestations that may indicate a specific hereditary syndrome (e.g. medullary thyroid cancer in patients with MEN 2), the decision to test a particular gene can also benefit from consideration of tumor location, the presence of metastases and the type of catecholamine produced by the tumor. PHEOs in patients

with *RET* mutations invariably have an adrenal location, very rarely present with malignant disease, and are always associated with increases in plasma levels or urinary excretion of metanephrine, the metabolite of epinephrine. Such increases may occur with or without parallel increases in normetanephrine. This biochemical pattern reflects expression of phenylethanolamine N-methyltransferase (PNMT), the enzyme that converts norepinephrine to epinephrine. This contrasts with PHEOs in patients with VHL gene mutations, which do not express PNMT, and which consequently do not produce epinephrine. PHEOs in this setting are therefore characterized by increases in plasma or urinary normetanephrine and normal levels of metanephrine. Similar to PHEOs in MEN 2, malignant disease is rare and bilateral adrenal tumors are relatively common. Relative to patients with RET mutations, extra-adrenal tumors in VHL patients are, however, more common.

Although mutations of SDHB and SDHD genes are occasionally associated with solitary adrenal tumors, patients with these mutations most commonly present with extra-adrenal PHEOs, often with multifocal disease. Patients with these mutations may also present with head and neck PGLs without biochemical evidence or signs and symptoms of a catecholamine-producing tumor. Testing for SDHD and SDHB gene mutations in patients with extra-adrenal tumors can therefore be particularly revealing; furthermore, because SDHB mutations carry a high risk for malignant disease, testing for such mutations in patients with metastases, especially from an extra-adrenal PGL, is particularly warranted. SDHB mutations have been mostly associated with abdominal, pelvic, and thoracic catecholamine-secreting familial PGL. Furthermore, the carriers are more likely to develop malignant PGLs and additional neoplasms, such as renal cell carcinoma, papillary thyroid tumors, neuroblastoma, or gastrointestinal stromal tumors (GIST). About 50% or more of SDHB mutation carriers will develop malignant PGLs, and up to 60% of patients with a malignant PGL harbor a SDHB mutation. The associated risk of malignancy varies significantly from one study to another, depending on the number of analyzed subjects and on the applied definitions of metastatic disease, including or not the sites where chromaffin tissue is normally present. In addition, more lifelong follow-up studies are needed, to correctly estimate the lifelong malignant risk in SDHB mutation carriers. Germ-line mutations of the SDHB, SDHC, and SDHD genes were also found in the Carney–Stratakis syndrome, an autosomal dominant disorder characterized by the dyad of PGLs and GIST. Other novel susceptibility loci for PHEOs are actively being investigated [34, 66].

Biochemical Diagnosis

It is known that catecholamines are metabolized within chromaffin cells to metanephrines (norepinephrine to normetanephrine and epinephrine to metanephrine) [65-70]. This intra-tumoral process occurs independently of catecholamine release, which can occur intermittently or at low rates. In line with these concepts, numerous independent studies have now confirmed that measurements of fractionated metanephrines (i.e. normetanephrine and metanephrine measured separately) in urine or plasma provide superior diagnostic sensitivity over measurement of the parent catecholamines.

Consequent to the above considerations, current recommendations are that initial testing or screening test for PHEO should include measurements of fractionated metanephrines in urine, plasma or both, as available [1-3, 74-78]. Although better diagnostic accuracy may be achieved using the plasma than the urine test, the difference is relatively small compared to differences of either test with the parent catecholamines. It should be noted that while an elevation of plasma or urinary normetanephrine slightly above the upper reference intervals may only marginally increase the pre- to post-test probability of PHEO, an elevation of more than 4-fold above those intervals is associated with close to 100% probability of the tumor. The actual level of the abnormal result should therefore be used to determine the need for immediate tumor localization studies versus additional biochemical investigations.

Table 4. Drugs that may cause false positive elevations of plasma and urinary catecholamines or metanephrines

	Catecholamines		Metanephrines	
	NE	**E**	**NMN**	**MN**
Tricyclic antidepressants Amitriptyline (Elavil), Imipramine (Topfranil), Nortriptyline (Aventyl)	+++	-	+++	-
-Blockers (non-selective)α Phenoxybenzamine (Dibenzyline)	+++	-	+++	-

Table 4. Drugs that may cause false positive elevations of plasma and urinary catecholamines or metanephrines				
	Catecholamines		**Metanephrines**	
	NE	**E**	**NMN**	**MN**
1-selective)α-Blockers (α Doxazosin (Cardura), Terazosin (Hytrin), Prazosin (Minipress)	+	-	-	-
ß-Blockers Atenolol (Tenormin), Metoprolol (Lopressor), Propranolol (Inderal), Labetolol (Normadyne)*	+	+	+	+
Calcium channel antagonists: Nifedipine (Procardia), Amlodipine (Norvasc), Diltiazem (Cardizem), Verapamil	+	+	-	-
Vasodilators: Hydralazine (Apresoline), Isosorbide (Isordil, Dilatrate), Minoxidil (Loniten)	+	-	unknown	unknown
Monoamine oxidase inhibitors: Phenelzine (Nardil), tranylcypromine (Parnate), Selegiline (Eldepryl)	-	-	+++	+++
Sympathomimetics: Ephedrine, Pseudoephedrine (Sudafd), Amphetamines, Albuterol (Proventil)	++	++	++	++
Stimulants: Caffeine (coffee*, tea), Nicotine (tobacco), Theophylline	++	++	unknown	unknown
Miscellaneous				
Levodopa, Carbidopa (Sinemet)*	++	-	unknown	unknown

Table 4. Drugs that may cause false positive elevations of plasma and urinary catecholamines or metanephrines				
	Catecholamines		Metanephrines	
	NE	E	NMN	MN
Cocaine	++	++	unknown	unknown

NE, norepinephrine; E, epinephrine; NMN, normetanephrine; MN, metanephrine. +++, substantial increase; ++, moderate increase; +, mild increase if any; - , little or no increase; *, indicates a drug that can also cause direct analytical interference with some methods. Adapted from Eisenhofer and Pacak (106).

The conditions under which blood or urine samples are collected can be crucial to the reliability and interpretation of test results (Table 4). Blood measurements of plasma free metanephrines or catecholamines should be collected with patients lying supine for at least 20 minutes before sampling. To avoid any stress associated with the needle stick, samples should ideally be collected through a previously inserted i.v. Patients should have refrained from nicotine and alcohol for at least 12 hours, and to minimize analytical interference should have fasted overnight before blood sampling. There is also often a need for patients to avoid acetaminophen for at least 5 days before sampling, but this requirement depends on the laboratory method used for measurements of plasma free metanephrines. Tricyclic antidepressants and phenoxybenzamine increase plasma and urinary norepinephrine and normetanephrine and represent the most common causes of medication-associated false-positive results in patients tested for PHEO (Table 4). A false-positive elevation of urinary normetanephrine due to sympathetic activation is also likely to be associated with false-positive elevations of urinary and plasma noradrenaline and plasma normetanephrine. While elevations in follow-up tests may serve to confirm the validity of the initial elevated test result, they may not always allow a PHEO to be distinguished from a state of sympathetic activation. In such situations, the clonidine suppression test combined with measurements of plasma catecholamines and normetanephrine is useful [79]. Clonidine is administered in a dose of 0.3 mg/70 kg of body weight orally. Lack of a decrease in norepinephrine or normetanephrine (below the upper reference limit or less than 50% or 40%, respectively compared to baseline value) 3 hrs after the administration of drug, is highly suggestive of a pheochromocytoma. Due to low sensitivity, the glucagon provocative testing has been abandoned [80].

In patients with renal failure, PHEO can be reliably excluded based on normal values for plasma free metanephrines; this is in contrast to conjugated metanephrines which are cleared by the kidneys and show large increases associated with renal failure [81]. Although measurements of plasma free normetanephrine and metanephrine provide a sensitive test for diagnosis of PHEO, (Table 5) these measurements may fail to detect tumors that produce predominantly dopamine (patients with these tumors usually do not present with any cardiovascular symptoms that are normally seen in tumors secreting epinephrine or norepinephrine). Such tumors are usually very rare and they are found extra-adrenally [82]. In such patients, measurements of plasma free methoxytyramine (metabolite of dopamine) or dopamine can be used to detect tumors; in contrast, measurements of urinary dopamine are much less reliable due to derivation of the urinary amine mainly from circulating dihydroxyphenylalanine, not dopamine [83]. Eisenhofer et al. established that free methoxytyramine is a novel marker for metastatic PHEO/PGL together with the presence of SDHB mutation, size (> 3cm) and extra-adrenal locations of primary tumors. He also demonstrated that it is a more sensitive biomarker of tumoral dopamine production and metastatic spread than either plasma or urinary dopamine [84]. A biochemical diagnosis of PGL is established by elevated concentrations of plasma and/or urine catecholamines and their O-methylated metabolites. Subsequently, tumors can then be localized by a combination of anatomic and functional imaging [85]. Patients with SDHB mutations may present with biochemically silent abdominal PGLs due to defective catecholamine synthesis resulting from the absence of tyrosine hydroxylase. Screening for tumors in patients with SDHB mutations should not be limited to biochemical tests of catecholamine excess.

Table 5.

Biochemical Test	**Sensitivity (%)**		**Specificity (%)**	
	Children	Adults	Children	Adults
Plasma normetanephrine and metanephrine	100	99	94	89
Plasma norepinephrine and epinephrine	92	84	91	81
Urinary normetanephrine and	100	97	95	69

metanephrine				
Urinary norepinephrine and epinephrine	100	86	83	88
Urinary vanillylmandelic acid	-	64	-	95

Children: Adapted from Weise *et al*. J Clin Endocrinol Metab 2002 (based on 45 children studied, 12 pheochromocytomas). Adult patients: Adapted from Zelinka *et al*. Stress 2007 and Lenders *et al*. JAMA 2002.

Tumor Localization

Tumor localization should usually only be initiated once the clinical evidence for PHEO/PGL is reasonably compelling, as may be indicated by strongly positive biochemical test results. In patients with a hereditary predisposition, a previous history of the tumor, or other presentations where the pre-test probability of a tumor is relatively high, less-compelling biochemical evidence might justify imaging studies.

Either computed tomography (CT) or magnetic resonance imaging (MRI) are recommended for initial tumor localization (more than 95% of tumors are found), with MRI preferred in children or pregnant women due to concerns regarding radiation exposure, patients with a documented allergy to contrast dye, or in situations where no additional radiation exposure is desired, and in the detection of extra-adrenal PHEO in a very unusual location [86]. Initial studies should initially focus on the abdomen and pelvis. If a tumor is not found, chest and neck images should be obtained, but with recognition that metastatic lesions in long bones can be missed.

Although CT and MRI have excellent sensitivity for detecting most catecholamine-producing tumors, these anatomical imaging approaches lack the specificity required to unequivocally identify a mass as a PHEO or PGL (Figure 1). The higher specificity of functional imaging offers an approach that overcomes the limitations of anatomical imaging, providing justification for the coupling of the two approaches (Figure 2) [86-87]. Functional imaging also allows determination of the extent of disease, including the presence of multiple tumors or metastases, information that can be important for appropriately guiding subsequent management and treatment.

^{123}I-MIBG is a guanethidine analogue resembling norepinephrine and therefore is concentrated by sympatho-adrenergic tissues especially chromaffin tissue of the adrenal medulla. ^{123}I-MIBG scintigraphy has been in use for PHEO diagnosis since 1981. Limits to this functional imaging include suboptimal sensitivity. Reduced sensitivity of MIBG scans particularly in familial PGL syndromes, malignancy and extra-adrenal PHEO has been described. Therefore a false-negative ^{123}I-MIBG SPECT in patients with PHEO or PGL follow a more aggressive course and are frequently linked to the presence of SDHB mutation. Fonte et al.reported that a false negative ^{123}I-MIBG SPECT is frequently related to metastatic tumors and usually due to SDHB mutations with unfavorable prognosis and recommended that patients with false-negative ^{123}I-MIBG SPECT be tested for SDHB mutations and undergo more regular and close follow-up [90]. Recently, different positron emission tomography (PET) reagents have been evaluated in such patient populations see Table 6 [91].

Table 6. Estimated functional imaging performance in some separate genotypes

	[$^{123/131}$I]MIBG	**specific PET ([^{18}F]FDA, [^{18}F]FDOPA)**	**non-specific PET ([^{18}F]FDG)**	**Selected references**
VHL	+	++	insufficient data	Kaji *et al*., Hoegerle *et al.*
MEN	+	+	insufficient data	Greenblatt *et al.*, Pacak *et al.*
SDHB	+/-	++	++ / ++++ #	Timmers *et al.* Timmers *et al.* Fonte *et al.*
SDHC	insufficient data	insufficient data	insufficient data	
SDHD	+	+ head and neck PGL	insufficient data	Van Houtum *et al.*

Legend: VHL= von Hippel-Lindau, MEN= multiple endocrine neoplasia, SDH=succinate dehydrogenase type B,C,or D, #=metastatic SDHB associated disease, °= several studies performed before discovery of succinate dehydrogenase gene mutations, SDH associated disease may present as sporadic.

In patients where ^{123}I-MIBG scanning is negative positron emission tomography (PET) or ^{111}In-octreotide scanning may be useful [89, 91, 92]. PET with ^{18}F-fluorodeoxyglucose, ^{18}F-fluorodopamine, ^{18}F-fluorodopa or ^{11}C-hydroxyephedrine are other useful functional imaging modalities which can be used as alternative for ^{123}I-MIBG

or as additional procedures when ^{123}I-MIBG returns negative results (Figure 2) [93-99]. Moreover ^{18}F-FDG PET/CT scanning is suitable for routine functional imaging of PHEOs and PGLs. Compared with ^{123}I-MIBG SPECT, ^{18}F-FDG PET allows better detection of metastases, provides a high specificity, and enables functional characterization of PHEO and PGL. The observations of a high ^{18}F-FDG uptake in SDHx and VHL-related tumors vs low uptake in MEN2-related tumors illustrate that functional imaging can provide important clues for a hereditary syndrome underlying PHEO and PGL [100]. However, this PET imaging agent can be useful where other imaging modalities are negative, often in rapidly growing metastatic tumors that have lost the ability to accumulate other agents [101]. It has been demonstrated to be superior to other functional imaging techniques in patients with metastatic SDHB-associated PHEO and PGL with sensitivity in this patient population approaching 100% [102].

^{18}F-Fluorodopamine PET offers excellent diagnostic sensitivity and spatial resolution, and appears particularly useful for localization of metastases. Recent studies demonstrate ^{18}F-Fluorodopamine PET/CT is the preferred technique for localization of primary PGLs and to rule out metastases if a genetic status is unknown. However, if unavailable, secondary and equivalent tests would be ^{18}F-fluorodihydroxyphenylalanine PET (^{18}F-FDOPA PET) and ^{123}I-MIBG. King et al reported that ^{18}F-FDOPA PET is the first line imaging agent for the localization and diagnosis of head and neck paragangliomas in SDHx-mutation carriers, regardless of biochemical phenotype. In the absence of ^{18}F-FDOPA PET, it is recommended the use of the more readily available ^{18}F-FDG PET/CT or ^{111}In- pentetreotide scintigraphy in combination with CT/MRI for proper anatomical localization.

PHEO and PGL have also shown to express somatostatin receptors (SSTR) both on *in vivo* imaging and *in vitro* studies. The single photon emission tomography (SPECT) agent ^{111}In-pentetreotide has been shown to be superior to ^{123}I-MIBG in patients with malignant, metastatic and extra-adrenal lesions. However, the overall sensitivity of this method is less than 30%. ^{68}Ga-labelled [1, 4, 7, 10– tetraazacyclododecane-1, 4, 7, 10-tetraacetic acid]-1- Nal^{3}-Octreotide (^{68}Ga-DOTA-NOC) is a positron emission tomography (PET) tracer for somatostatin receptor scintigraphy (SRS), which provides the advantages of better resolution and quantification, of PET technology. Recent studies demonstrated that ^{68}Ga- DOTA-NOC PET/CT is an imaging technique that provides high sensitivity and specificity in the detection of PHEO/PGL and is superior to ^{123}I-MIBG scintigraphy. ^{68}Ga-DOTA-NOC PET-CT has the potential to become the functional imaging method of choice [103].

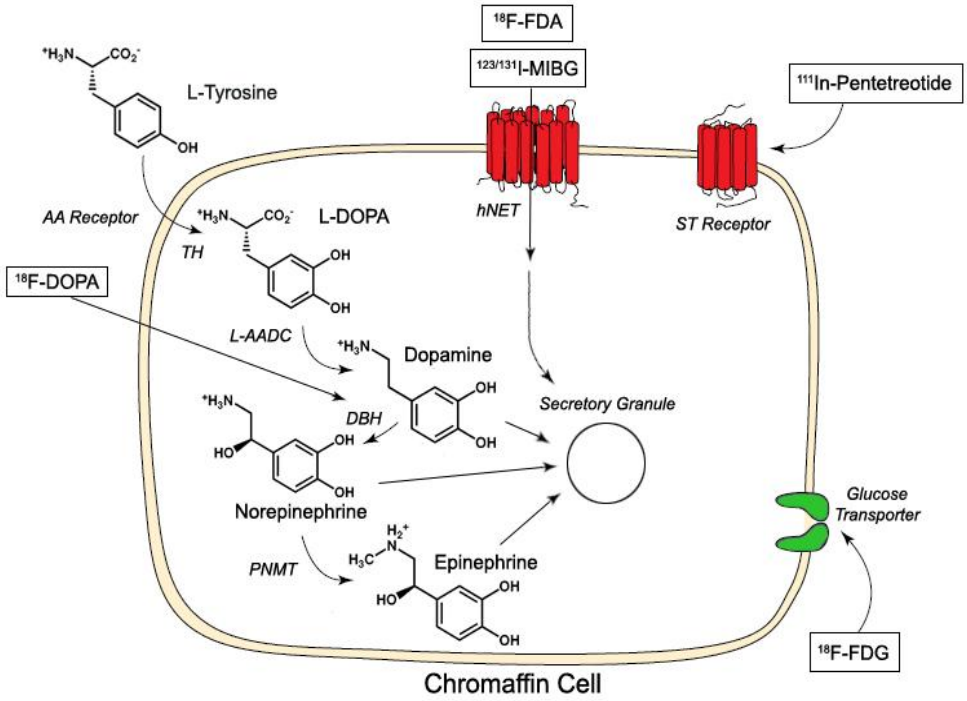

Figure 1. Chromaffin cell and its targets for functional imaging.

Adapted by Kyle Horak, from: Ilias *et al.* [71]

Legend: *AA Receptor* = Aminoacid receptor, *hNET* = (human) norepinephrine transporter, *ST Receptor* = somatostatin receptor, *Glucose Transporter* = GLUT 1 receptor, *TH* = tyrosine hydroxylase, *L-AADC* = L-aromatic-aminoacid decarboxylase, *DBH* = dopamine-β-hydroxylase, *PNMT* = phenylethanolamine-N-methyltransferase.

There is some debate about whether functional imaging should be used in PHEOs (particularly those located in the adrenal gland); especially after CT or MRI was performed. Several important considerations impact the choice of additional functional imaging studies. First, although this tumor is most often localized in the adrenal gland, the adrenal gland is also the site of many benign adrenal tumors (adenomas); in the general population between 5-10% may be expected to have such masses, this is dependent on age. Second, about 50% of adrenal PHEOs produce near exclusively norepinephrine, this representing the same pattern as in extra-adrenal PHEOs. Thus,

whereas production of epinephrine (best detected by an increase in metanephrine) indicates an adrenal location, exclusive production of norepinephrine (best indicated by increases of normetanephrine with normal metanephrine) may reflect either an adrenal or extra-adrenal location. Third, about 10% of patients have metastatic PHEOs at initial diagnosis; those with primary tumors larger than 5 cm are at particular risk. Fourth, in patients with previous surgeries (especially in the abdomen) the presence of post-surgical tissue changes (e.g. tissue fibrosis, adhesions) and surgical clips often precludes correct localization of recurrent or metastatic PHEOs using CT or MRI. Fifth, up to 24% of PHEOs are familial and these tumors are often multiple. Based on the above we advise additional use of functional imaging studies for localization of most cases of biochemically proven PHEO. Exceptions may include small (less than 5 cm) adrenal masses associated with elevations of plasma or urine metanephrine (practically all epinephrine-producing PHEOs are found in the adrenal gland or are recurrences of previously resected adrenal tumors.

Management of Pheochromocytoma

The definitive treatment of PHEO is surgical excision of the tumor. Laparoscopic surgery is commonly the technique of first choice for resection adrenal and extra-adrenal PHEOs when oncologic principles can be followed. Preparation of the patient for surgery requires adequate preoperative medical treatment to minimize operative and postoperative complications [18, 26, 104]. Exposure to high levels of circulating catecholamines during surgery may cause hypertensive crises and arrhythmias, which can occur even when patients are preoperatively normotensive and asymptomatic. All patients with PHEO should therefore receive appropriate preoperative medical management to block the effects of released catecholamines.

Phenoxybenzamine (Dibenzyline), an α-adrenoceptor blocker, is most commonly used for preoperative control of blood pressure. The drug is administered orally at a dose of 10-20 mg twice daily for 2 weeks before surgery. At some centers, a supplemental dose (0.5-1.0 mg/kg) is administered at midnight before surgery, in which case appropriate safeguards are required to avoid orthostatic hypotension. Intravenous fluids may be administered if there is concern that blood volume has not been adequately replaced. Alternatives to phenoxybenzamine for preoperative blockade of catecholamine-induced vasoconstriction include calcium channel blockers and selective α_1-adrenoceptor blocking agents, such as terazosin (Hytrin) and doxazosin (Cardura).

A α-adrenoceptor blocker may be used for preoperative control of arrhythmias, tachycardia or angina. However, loss of α-adrenoceptor-mediated vasodilatation in a patient with unopposed catecholamine-induced vasoconstriction can result in dangerous increases in blood pressure (sometimes hypertensive crisis). Therefore, α-adrenoceptor blockers should never be employed without first blocking α-adrenoceptor mediated vasoconstriction.

In some patients blood pressure can reach very high values and such a situation is termed a hypertensive crisis when it is life-threatening or compromises vital organ function [105]. The hypertensive crises are the result of a rapid and marked release of catecholamines from the tumor. Patients may experience hypertensive crises in different ways. Some report severe headaches or diaphoresis, while others have visual disturbances, palpitations, encephalopathy, acute myocardial infarction, congestive heart failure, or cerebrovascular accidents. Therefore, it is crucial to start proper antihypertensive therapy immediately. Treatment of a hypertensive crisis due to PHEO should be based on administration of phentolamine. It is usually given as an i.v. bolus of 2.5 mg to 5 mg at 1 mg/min. If necessary, phentolamine's short half-time allows this dose to be repeated every 5 minutes until hypertension is adequately controlled. Phentolamine can also be given as a continuous infusion (100 mg of phentolamine in 500 mL of 5% dextrose in water) with an infusion rate adjusted to the patient's blood pressure during continuous blood pressure monitoring. Alternatively, control of blood pressure may be achieved by a continuous infusion of sodium nitroprusside (preparation similar to phentolamine) at 0.5 to 10.0 μg/kg per minute (stop if no results are seen after 10 minutes) [23, 106].

In all patients before surgery and in some patients on whom elevated blood pressure and arrhythmia cannot be controlled by using a and ß blockade, α-methyl-*para*-tyrosine (metyrosine, Demser™), a competitive inhibitor of tyrosine hydroxylase, is used (the starting dose is usually 250 mg twice to fourth time a day). As reviewed in detail by Bravo and Gifford to ensure adequate preoperative preparation, several criteria should be fulfilled: (a) blood pressure not greater than 160/90 mm Hg; (b) orthostatic hypotension not below 80/45 mm Hg; and (c) no more than one ventricular extrasystole every 5 minutes and EKG without nonspecific ST segment elevations or depression and T wave inversions [23]. See Figure 2

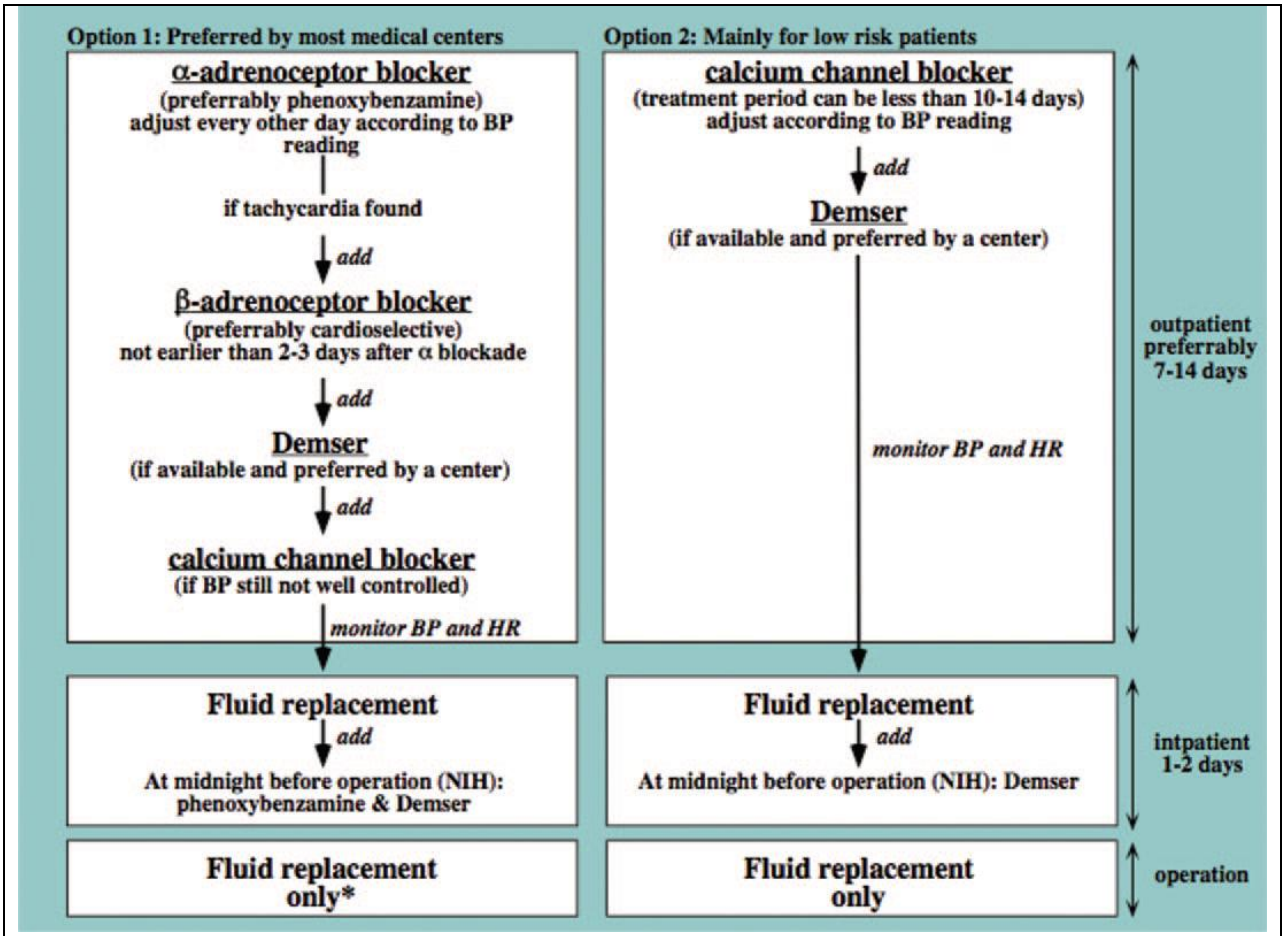

FIG. 2. Current recommended preoperative treatment algorithms in patients with pheochromocytoma. BP, Blood pressure; HR, heart rate. *
If alpha1-adrenoceptor blockers are used, then give one dose in the morning before surgery.

Although a few patients remain hypertensive in the immediate post-operative period, most require treatment for hypotension, which is best remedied by administration of fluids. Hypoglycemia in the period immediately after tumor removal is another problem that is best prevented by infusion of 5% dextrose started immediately after tumor removal and continuing for several hours thereafter. Post-operative hypoglycemia is transient, whereas low blood pressure and orthostatic hypotension may persist for up to a day or more after surgery and require care with assumption of sitting or upright posture.

There are known drug interactions in patients harboring PHEOs. Some drugs are more obvious due to their mechanism of action, such as dopamine D2 receptor antagonists such as metoclopramide or veralipride and beta-adrenergic receptor antagonists (beta-blockers). More recently, peptide and corticosteroid hormones,

including corticotropin, glucagon and glucocorticoids have been shown to have adverse reactions in this patient population [107]. Other classes of drugs contraindicated in patients with PHEO are tricyclic anti-depressants, other anti-depressants that are serotonin or norepinephrine reuptake inhibitors like Cymbalta and Effexor. Displacement of catecholamines from storage can have devastating sequelae. Many drugs for obesity management fall in this category such as phentermine (Adipex, Fastin and Zantryl), phendimetrazine (Bontril, Adipost, Plegine), sibutramine (Meridia), methamphetamine (Desoxyn) and phenylethylamine (Fenphedra). Other over the counter medications such as nasal decongestants containing ephedrine, pseudoephedrine, or phenylproanolamine can also lead to drug interference [30].

The long-term prognosis of patients after operation for PHEO is excellent, although nearly 50% may remain hypertensive after surgery. Biochemical testing should be repeated after about 14-28 days from surgery in order to check for remaining disease. Importantly, however, normal postoperative biochemical test results do not exclude remaining microscopic disease so that patients should not be misinformed that they are cured and that no further follow-up is necessary. On long-term follow-up about 17% of tumors recur, with about half of these showing signs of malignancy. Although follow-up is especially important for patients identified with mutations of disease-causing genes, there is currently no method based on pathological examination of a resected tumor to rule out potential for malignancy or recurrence. Thus, long-term periodic follow-up remains recommended for all cases of PHEO or PGL.

Malignant Pheochromocytoma

The incidence of metastatic PHEO ranges from 3% to 36% or even higher, depending on the genetic background and location of the primary tumor [11, 12, 108-110]. Location of metastatic lesions appears affect patient's survival. Short-term survivors (less than 5 years) tend to be patients with metastatic lesions in liver and lungs, whereas long-term survivors are those with metastatic lesions in bones [94, 95]. The overall 5-year survival rate varies between 34% and 60% but some recent data suggest a better survival (unpublished observations). This poor prognosis emphasizes the need to adequately identify either those patients with already existing metastatic disease or, preferably, those who may develop metastases. Currently, however, except for the presence of the *SDHB* mutation, large size (>3 cm) or an extra-adrenal location of

the primary tumor, and high methoxytyramine levels, there are no reliable markers for predicting a high likelihood of developing metastatic disease [21].

Although several therapeutic options exist for patients with metastatic PHEO, all are limited and there is no cure. Less than 40% of patients with metastatic PHEO respond (mostly partial remission) to currently used therapeutic modalities such as ^{131}I-MIBG or chemotherapy. Tumor size reduction palliates symptoms, but a survival advantage of debulking has not been proven. However, reduced tumor burden can facilitate subsequent radiotherapy or chemotherapy, but again this is not proven. External-beam irradiations of bone metastases, tumor embolization, or radiofrequency ablation to liver metastases provide some treatment alternatives. Chemotherapy with a combination of cyclophosphamide, vincristine and dacarbazine (so called CVD chemotherapy) can provide tumor regression and symptom relief in up to 50% of patients, but the responses are usually short in duration and there was no survival advantage reported [113, 114]**.** Recently, this regimen has been reported to be particularly effective in patients with the metastatic SDHB mutation related PHEOs or PGLs [115].

To date, ^{131}I-MIBG therapy is the single most valuable adjunct to surgical treatment of malignant PHEOs. Results of a phase II trial using high dose 131I-MIBG demonstrated 22% partial or complete response and 35% of patients having some degree of response (i.e. biochemical) without demonstrated progressive disease [116]. As a single agent ^{131}I-MIBG has limited efficacy for cure, and there is no consensus on what doses to use for treating either bone or organ metastases [117]. Approximately 60% of malignant PHEOs and PGLs express MIBG uptake and are therefore good candidates for ^{131}I-MIBG therapy. Previously published articles state chemo- or ^{131}I-MIBG therapy should be initiated only in patients in whom the quality of life is affected or metastatic lesions are growing aggressively and affect local surrounding tissue, it is our personal opinion that all patients with metastatic PHEO should be evaluated and considered for immediate treatment.

Clinicians using the above therapies, particularly chemotherapy, should be aware of potentially fatal complications arising from excessive catecholamine release as tumor cells are destroyed (usually within the first 24 hr). A major complication is bone marrow suppression usually 4 weeks after initiation of radioactive ^{131}MIBG and the severity of this varies in a dose-dependent fashion. Octreotide therapy is also available for malignant PHEO, however, the experience with this therapy is very limited with reports showing different responses [118]. Therefore, we recommend this treatment option to be used only in patients in whom chemo- or MIBG therapy cannot be carried out (e.g.

negative MIBG scan or severe bone marrow suppression). Octreotide therapy requires positive Octreoscan. As explained previously, PHEO/PGL express somatostatin receptors in high density. Therefore treatment with the radiolabeled somastotatin analogue DOTATOC is an option in somatostatin receptor positive PGL. However, the therapy seems to be less effective than in gastroentero-pancreatic neuroendocrine tumors. Nevertheless, DOTATOC appears to be a treatment option for surgically incurable PGLs, because toxicity is very low and especially the fact that long lasting remissions could be achieved justifies the treatment. [119].

There have been many other exploratory regimens that have emerged in the setting of targeted therapy. Most of these have been examined in the setting of metastatic neuroendocrine tumors in which between one and four cases in each cohort has included metastatic PHEO patients. While active research continues, patients when possible should be enrolled in trials to evaluate emerging regimens [120].

Take Home Points:

1. Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are neural crest-derived tumors, currently more than 40% have a known genetic cause. Thus, all patients with PPGLs should be considered for genetic testing. Recently new syndromes were described associated with these tumors: Carney-Stratakis syndrome; Pacak-Zhuang syndrome.
2. Genes to be tested should be based on several considerations: syndromic features, family history, age at diagnosis, multifocal and metastatic presentation, tumor location and a specific biochemical phenotype.
3. PHEOs are tumors that are mainly diagnosed based on the measurement of plasma or urinary metanephrines and methoxytyramine since 30% of these tumors do not secrete catecholamines.
4. Patients with metastatic disease should undergo testing for SDHB mutations.
5. Computed tomography (CT) is the first choice imaging modality. Magnetic resonance imaging (MRI) is recommended in patients with metastatic PHEO and PGL, for detection of skull base and neck PGLs, in patients with surgical clips that cause artifacts when using CT, in patients with an allergy to CT contrast, and in patients in whom radiation exposure should be limited (children, pregnant women, patients with known germline mutations and those with recent excessive radiation exposure).
6. ^{18}F-FDG PET/CT scanning in patients with metastatic disease.
7. ^{123}I-MIBG scintigraphy as a functional imaging modality in patients with metastatic

PHEO/PGL detected by other imaging modalities when radiotherapy using ^{131}I-MIBG is planned.

8. All patients with a hormonally functional PHEO or PGL should undergo preo perative blockade with α-adrenergic receptor blockers as the first choice to prevent perioperative cardiovascular complications for 7-14 days.
9. Minimally invasive adrenalectomy is recommended for most adrenal PHEOs and open resection for large or invasive PHEOs to ensure complete resection and avoid local recurrence.
10. Multidisciplinary teams at centers with appropiate expertise to ensure favorable outcome should treat all patients with PHEO and PGL.

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