Pheochromocytoma and Paraganglioma

Diagnosis, Genetics, and Treatment

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KEYWORDS

• Neuroendocrine tumor • Pheochromocytoma • Paraganglioma
• Biochemical evaluation • Genetics • Imaging • Perioperative management • Surgery

KEY POINTS

- Pheochromocytomas and paragangliomas (Pheo/PGL) are rare neuroendocrine tumors that are being discovered incidentally at an increasing rate.
- At least one-quarter of patients with Pheo/PGL display germline mutations; genetic testing plays an increasingly important role in the evaluation and management of these patients.
- Plasma-free metanephrines and urinary fractionated metanephrine levels are highly sensitive in the diagnosis of Pheo/PGL.
- Selective or nonselective alpha blocking agents and calcium channel blockers appear to be equally effective in treating the physiologic effects of Pheo/PGL.
- Several surgical approaches are used to remove Pheo/PGL, and the choice of approach depends on patient and tumor-related factors, as well as surgeon preference.

INTRODUCTION: NATURE OF THE PROBLEM

The terms paraganglioma (PGL) and pheochromocytoma (Pheo) were first mentioned in 1908 and 1912 respectively when pathologists Henri Alezais, Felix Peyron, and Ludwig Pick noted tumors with a positive chromaffin reaction in extra-adrenal and adrenal chromaffin tissue. However, according to Welborne and colleagues[1] it was not until 1922, when Marcel Labbe and colleagues[2] reported a case of symptomatic paroxysmal hypertension in a patient with a Pheo, that the relationship between the tumor and its symptoms was established.

The first successful resection for Pheo was performed by Cesar Roux in February 1926. The patient, Madam S, was 33 years old and had suffered attacks of vertigo

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and nausea for 2 years. At laparotomy, she was found to have a 13-cm adrenal Pheo. Charles Mayo performed the second and perhaps better-known resection for Pheo in October 1926. The patient, Mother Joachim, a nun from Canada, suffered from paroxysmal hypertension, weakness, vomiting, and headaches. At the time, it was felt that her hypertension was mediated through the sympathetic nerves and that sympathectomy may provide relief. She underwent an exploratory laparotomy, and a tumor "the size of a lemon" was found behind the tail of her pancreas. Without preoperative pharmacologic blockade, the entire procedure was completed in 64 minutes and the patient recovered well.[1,3]

By 1934, more than 60 patients had been diagnosed with a Pheo or PGL and by 1940, 20 successful operations had been performed. The operative mortality in these early series was 30% to 45%.[4] These high mortality rates were partly due to a lack of preoperative alpha blockade and modern anesthesia management. Since that time, much has been learned about the management of these rare tumors. Herein we discuss the incidence and prevalence of Pheo/PGL; describe the typical clinical presentation and diagnostic evaluation of these tumors; explore the known genetic associations; and summarize the preoperative, intraoperative, and postoperative management strategies.

EPIDEMIOLOGY

The annual incidence of Pheo and PGL is between 2 and 8 per million and the prevalence in the population is 1:6500 to 1:2500, respectively.[5] Pheo/PGLs are thought to occur in 0.05% to 0.1% of patients with sustained hypertension. However, this accounts for only 50% of people with Pheo/PGL because approximately half of patients will have paroxysmal hypertension or normotension.[5] Pheochromocytomas comprise 4% to 8% of all adrenal incidentalomas.[6–9] The peak age of occurrence is in the third to fifth decade of life. Today, 10% to 49% of Pheo/PGLs are found incidentally during imaging studies obtained for other reasons.[10–14]

In 1951, John Graham[15] analyzed the records of 207 Pheo/PGLs and concluded that Pheo/PGLs follow the "rule of 10s," with 10% occurring in extra-adrenal tissues, 10% bilateral, and 10% malignant. Later, the teaching that 10% of these tumors were familial was added to this rule. Although this teaching persists in many textbooks and medical school lectures, studies have shown that the "rule of 10" no longer applies. Approximately 15% to 25% of Pheo/PGLs originate in extra-adrenal chromaffin tissue,[16,17] 8% of sporadic and 20% to 75% of hereditary Pheo/PGL are bilateral at presentation,[18–20] 5% of adrenal-based and 33% extra-adrenal tumors are malignant,[14] and at least 24% of sporadic Pheo/PGLs have a genetic basis.[18] Today, bilaterality, extra-adrenal location, and prevalence of malignancy depend directly on the underlying genetic mutation.

PATHOPHYSIOLOGY

Pheo/PGLs are neuroendocrine tumors that arise from paraganglia cells derived from the neural crest and are distributed along the paravertebral and para-aortic axis from the base of the skull to the pelvic floor. Adrenal-based Pheos arise in the sympathetic adrenal chromaffin cells. Extra-adrenal sympathetic PGLs most commonly occur around the inferior mesenteric artery or at the aortic bifurcation in the organ of Zuckerkandl, but can occur in any chromaffin tissue in the thorax, abdomen, and pelvis. Almost all adrenal-based Pheos and extra-adrenal sympathetic PGLs produce, store, metabolize, and secrete catecholamines or their metabolites.[5] Extra-adrenal parasympathetic PGLs are most commonly found in the head and neck region and are

usually not associated with catecholamine secretion. In this article, head and neck PGLs are not discussed.

The uncontrolled release of catecholamines by Pheo/PGLs leads to several physiologic changes and end-organ effects. Prolonged and repeated norepinephrine release has been associated with long periods of vasoconstriction and contraction of the venous pool, and thus decreased circulating blood volume. The decrease in blood volume can lead to acute hypovolemia on cessation of norepinephrine-induced vasoconstriction when the Pheo/PGL is surgically removed. Tumors that secrete predominantly epinephrine have been associated with tachycardia and tachyarrhythmias in addition to arterial hypertension.[21] Elevated plasma catecholamine levels can result in increased glycogenolysis and inhibition of insulin release by islet cells, resulting in signs and symptoms of diabetes mellitus. Additionally, elevated catecholamines can lead to stress-induced cardiomyopathy (Takotsubo cardiomyopathy) with severe left ventricular dysfunction.[22] Pheochromocytoma crisis is the name given to a constellation of symptoms that can result from uncontrolled release of catecholamines and consists of multisystem organ failure, high fever, encephalopathy, and severe hypertension and/or hypotension. Although rarely seen today, these symptoms can progress to severe metabolic acidosis and death if not recognized and treated.[23]

CLINICAL PRESENTATION AND DIAGNOSIS

Clinical Presentation

The main signs and symptoms of excess circulating catecholamines from Pheo/PGL are headache, palpitations, sweating, pallor, nausea, constipation, flushing, weight loss, fatigue, anxiety, sustained or paroxysmal hypertension, orthostatic hypotension, fever, and hyperglycemia.[5,14] According to the degree of catecholamine excess, patients may present with myocardial infarction, arrhythmia, or stroke. Because similar signs and symptoms are produced by numerous other clinical conditions (**Table 1**), Pheo/PGL is often referred to as the "great mimic."[5] In our experience, patients are often diagnosed with an incidental "asymptomatic" adrenal mass and when a focused history is obtained, the classic symptoms of Pheo/PGL are often elicited in retrospect.

Biochemical Evaluation

Traditional biochemical tests include measurements of urinary and plasma catecholamines, urinary fractionated and plasma-free metanephrines, and urinary vanillylmandelic acid (VMA). When a patient is suspected to have a Pheo/PGL, the recommended initial test is plasma-free metanephrines or 24-hour urinary fractionated metanephrines.[5,14,24] Norepinephrine and epinephrine are metabolized within the tumor by

Table 1
Differential diagnosis for diagnosis of pheochromocytoma and paraganglioma

Organ System	Possible Diagnosis
Endocrine	Hyperthyroidism, carcinoid syndrome, hypoglycemia, medullary thyroid carcinoma, mastocytosis, menopause
Cardiovascular	Congestive heart failure, arrhythmias, ischemic heart disease, baroreflex failure
Neurologic	Migraine, stroke, meningioma, postural orthostatic tachycardia
Miscellaneous	Porphyria, panic disorder, factitious disorders, monoamine oxidase inhibitor use, clonidine withdrawal, cocaine abuse

catechol-*O*-methyltransferase to normetanephrine and metanephrine, respectively.[25] The lack of this enzyme in sympathetic nerves means that the O-methylated metabolites are relatively specific markers of chromaffin tumors.[26] These metabolites are produced continuously in the tumor independent of physiologic catecholamine release and therefore have been shown to be both more sensitive and specific diagnostic biomarkers of Pheo/PGL than their parent catecholamine.[5,27,28] There is no consensus that one test is superior.[26] The investigators prefer to start by measuring plasma-free metanephrines because of their high sensitivity and patient convenience. Blood sampling should be performed with the patient in the supine position 15 to 20 minutes after intravenous (IV) catheter insertion. Eight to 12 hours before testing, food, caffeinated beverages, strenuous exercise, and/or smoking should be avoided, to reduce false-positive results from secondary catecholamine release. Providers interpreting tests results should be aware that sympathomimetic agents such as labetalol, sotalol, acetaminophen, buspirone, mesalamine, sulfasalazine, methyldopa, and antidepressants can interfere with the biochemical assays.[25,29] In a multicenter cohort study of 858 patients, Lenders and colleagues[27] found that the use of multiple initial diagnostic tests increases sensitivity at the cost of decreased specificity. A single plasma or urine metanephrine level remains superior to that of a combination of biochemical tests for initial diagnostic workup.

Studies have shown that in comparison with plasma-free metanephrines or urinary fractionated metanephrines, urinary VMA has a lower sensitivity (68%) and therefore it is not used routinely in our practice.[26] Plasma or urinary dopamine and its metabolite (methoxytyramine) may also be elevated in patients with Pheo/PGL. Although they are not used for diagnostic purposes, their elevation has been associated with SDHB and SDHD mutations and therefore may help guide management.[30]

A suggested algorithm for the biochemical evaluation of Pheo/PGL is depicted in **Fig. 1**. If urine and/or plasma metabolites are normal, the diagnosis of Pheo/PGL can be excluded due to the high sensitivity of these tests. If urine and/or plasma metabolite levels are >4 times above the upper limit of normal for any given laboratory, the diagnosis of Pheo/PGL is highly probable.[5,25,31] Patients with slight or moderate elevation (>1 time or less than 3 times above the normal limit) of both or either metabolite should undergo repeat testing once potential causes of false-positive results are removed or addressed. Finally, if repeat testing results in elevation of metabolites, a clonidine suppression test can be considered to confirm the diagnosis. This test is useful in distinguishing between high levels of plasma norepinephrine caused by release from sympathetic nerves and those from Pheo/PGL. It is considered diagnostic if norepinephrine levels remain elevated 3 hours after administration of 0.3 mg of oral clonidine.[25] It is important to note that this test is not useful for tumors that intermittently secrete catecholamines or in patients who have marginally elevated norepinephrine levels. Additionally, diuretics and tricyclic antidepressants can cause false-positive values.[16] When the diagnosis of Pheo/PGL is suspected but not confirmed (lack of >4 times elevation of metabolites) and there is a mass on imaging, our group prefers to forgo the clonidine test and proceed directly to resection, particularly when such patients have indications for surgical intervention, such as a large size and atypical imaging characteristics.[32]

When possible, biochemical testing should always precede imaging, as it is the most cost-effective approach to the diagnosis of Pheo/PGL and if biochemical testing proves negative, the patient is not subject to unnecessary radiation. However, in clinical practice, many patients with Pheo/PGL present with an incidentally discovered mass and are in need of biochemical evaluation after imaging is already complete.[5,26,32]

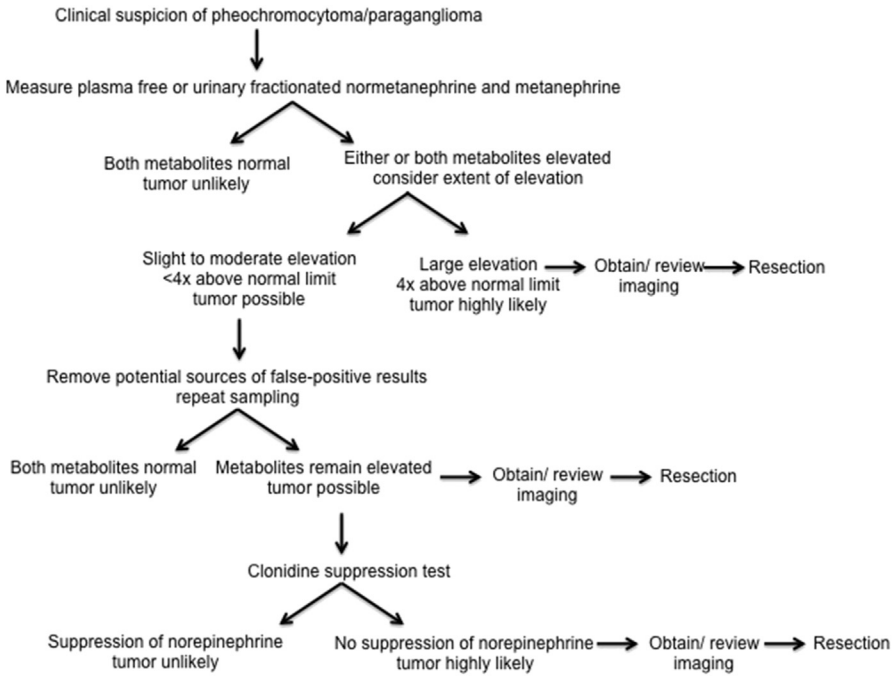

Fig. 1. Algorithm for the biochemical evaluation of Pheo/PGL.

Imaging

The 2 most commonly used imaging modalities in the initial evaluation of Pheo/PGL are computerized tomography scan (CT) with and without IV contrast (adrenal protocol for adrenal lesions) and MRI. Functional imaging, including 123 I-metaiodobenzylguanidine (MIBG), 111-In-Pentetreotide (octreotide scan), and PET combined with CT (PET/CT) using fluorodeoxyglucose (FDG) and other radiolabeled agents are also used for the localization of Pheo/PGL.

Computed tomography

CT provides an excellent initial method for the localization of Pheo/PGL because of its outstanding spatial resolution for the thorax, abdomen, and pelvis. To obtain the best results, CT scans should be performed with and without IV contrast. CT scans are highly sensitive (88%–100%) but lack specificity.[26,33] Pheo/PGL may appear homogeneous or heterogenous, can be necrotic with some calcifications, and may appear solid or cystic (**Fig. 2**A). Pheo/PGLs demonstrate avid contrast enhancement due to their rich capillary network, and most exhibit mean attenuations of more than 10 Hounsfield units on unenhanced CT.[32,34] Some studies suggest that the sensitivity of CT for extra-adrenal or bilateral tumors can be low, and therefore the use of MRI or other functional studies is advised in these populations.[35,36] However, in our practice, CT scan is often the only imaging study necessary to localize lesions and plan for resection of a Pheo/PGL.

MRI

This imaging technique has the same sensitivity and specificity as CT scan in detecting adrenal-based Pheos but has shown superior sensitivity (near 100%) in detecting PGLs and familial adrenal pheochromocytomas.[37] Pheo/PGLs show enhancement on

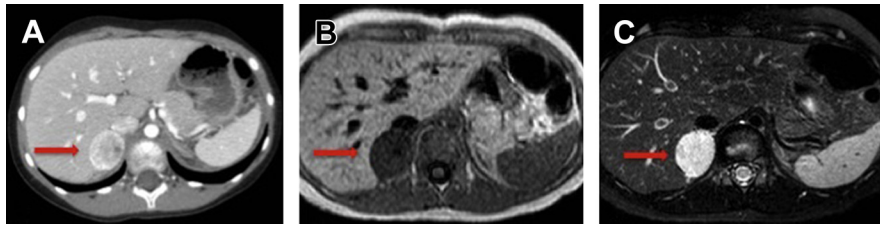

Fig. 2. CT and MRI images of adrenal-based Pheo. (*A*) CT abdomen with IV contrast of right adrenal pheochromocytoma. (*B*) MRI T1-weighted image of right Pheo. (*C*) MRI T2-weighted image of right adrenal Pheo. *Arrows* point to the adrenal based pheochromocytoma.

T2-weighted imaging and may appear heterogenous due to internal hemorrhage and cystic components (Fig. 2B, C).[34] MRI is useful in patients with inability to tolerate IV contrast, those with intracorporeal metal or surgical clips, and in patients in whom radiation exposure should be limited; that is, children, pregnant women, patients with germline mutations, or in patients with previous excessive radiation exposure.[26]

Functional imaging

There is debate over the role of functional imaging in the preoperative evaluation of Pheo/PGL. Some groups recommend functional imaging for all Pheo/PGLs except for metanephrine producing a small adrenal-based Pheo (PGLs do not produce epinephrine).[5] Others recommend selective use of functional imaging for patients with a high risk of recurrent, multifocal, or malignant disease and for patients with occult lesions on CT or MRI.[38,39] The field of functional imaging is expanding and some techniques are available only under clinical trials at selected centers.

Metaiodobenzylguanidine with single-photon emission computed tomography

Metaiodobenzylguanidine with single-photon emission CT (MIBG-SPECT) is a guanethidine analog resembling norepinephrine that is taken up and concentrated in sympatho-adrenergic tissue. SPECT data can be fused with CT images to improve spatial resolution and provide anatomic correlation (Fig. 3). The 123 I-MIBG is used preferentially over 131 I-MIBG because of its higher sensitivity, shorter half-life, lack of beta emission, lower radiation dose, and better image quality. The 131 I-MIBG can be used to treat MIBG avid metastasis. MIBG displays improved specificity (95%–100%) when compared with CT or MRI. MIBG can be used to identify sites of primary disease, evaluate metastases, and confirm the biochemical diagnosis. However, 123 I-MIBG-SPECT has lower sensitivity (80%–100%, 88%–100%, respectively) when compared with MRI and CT.[26,39–41] Some studies show that the sensitivity of MIBG scans is further reduced in familial PGL syndromes, malignant disease, and extra-adrenal Pheo/PGLs[5,41–45] (Fig. 4). Furthermore, up to 50% of normal adrenal

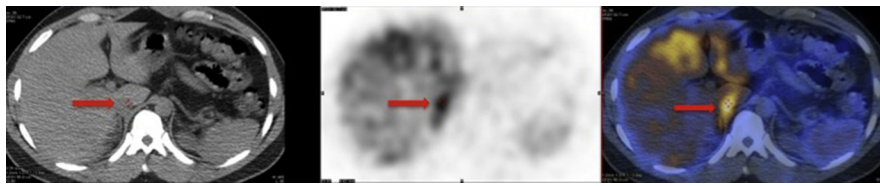

Fig. 3. CT, MIBG, and MIBG with SPECT/CT fusion of right adrenal-based Pheo. From left to right, CT scan, MIBG, MIBG with SPECT/CT fusion. *Arrows* point to the adrenal based pheochromocytoma.

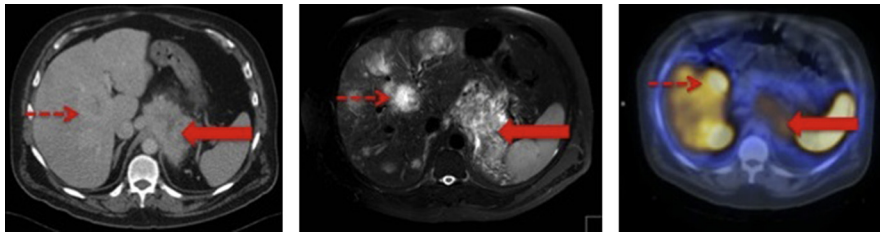

Fig. 4. CT, MRI, and MIBG-SPECT/CT of para-aortic PGL with liver metastases (*solid arrow* points to PGL; *dashed arrow* points to liver metastases.) From left to right: CT scan of abdomen and pelvis, MRI T2-weighted image, MIBG-SPECT/CT.

glands demonstrate physiologic uptake of 123 I-MIBG and thus false-positive results for adrenal-based lesions are a problem.[26,46]

Octreotide scan

The radiolabeled octreotide binds to somatostatin receptors in tumors; however, the extent of the binding is variable and dependent on the presence of such receptors in the Pheo/PGL.

The 123 I-MIBG is more sensitive than octreotide for the site of primary disease; however, octreotide has high sensitivity for metastatic disease and can be positive in tumors that have no MIBG uptake. Therefore, octreotide scans may be useful if MIBG scan is negative and/or metastatic disease is suspected.[34]

PET/computed tomography scan

Depending on the radioactive tracer used, the use of PET/CT scans in Pheo/PGL can have superior sensitivity and specificity when compared with 123 I-MIBG and octreotide scans.

However, because of its limited availability and sometimes high cost, it is not commonly used in the evaluation of Pheo/PGL.[26] There are multiple agents used in PET scanning for Pheo/PGL and include 18F-FDG, 18F-fluorodopamine (18F-FDA), 18-F-fluorodihydroxy-phenylalanine (18F-FDOPA) and 68-gallium 1,4,7,10-teraazacyclododecane-1,4,5,10-teraacetic acid-octreotate (68-Ga-DOTATATE). The currently known strengths and weaknesses of these imaging agents and the aforementioned imaging modalities are summarized in **Table 2**.

Although some investigators advocate for both positive localization with CT/MRI and 123-MIBG before surgical intervention,[16] most investigators will agree that when there is a high biochemical probability of Pheo/PGL and low likelihood of metastases (small tumor, adrenal location, adrenergic phenotype, non-*SDHB*) that CT or MRI is adequate. If, however, metastatic disease is suspected or when CT or MRI fails to localize the lesion, functional imaging may be warranted.[5,26,47] In our practice, if CT or MRI fails to localize the lesion or a patient is suspected to have a hereditary syndrome or metastatic disease, 123-MIBG, 18F-FDG, or 68-Ga-DOTATATE (on protocol) or a combination may be used.

Genetic Testing

Pheo/PGLs are associated with multiple genetic mutations and familial syndromes (**Table 3**). It is estimated that 20% to 41% of Pheo/PGLs are associated with known genetic mutations.[48–51] Neumann and colleagues[18] studied 298 unrelated patients diagnosed with presumably sporadic Pheo/PGL, and 24% were found to have germline mutations. Hereditary Pheo/PGLs are most commonly associated with Multiple

Table 2
Diagnostic imaging modalities: strengths and weaknesses

	Strengths	Weakness
CT with and without IV contrast	• Localizes Pheo/PGL with 88%–100% sensitivity • Easiest for surgeon to interpret • Often the only imaging modality necessary to localize and plan for resection	• Lacks specificity • Lower sensitivity (64%) for extra-adrenal or bilateral tumors • Requires IV contrast
MRI	• Localizes Pheo/PGL with 88%–100% sensitivity • Localizes extra-adrenal and familial adrenal Pheo/PGL with near 100% sensitivity • Avoids radiation exposure of CT	• Difficult to interpret for surgical planning • Less tolerated by some patients (claustrophobia)
123 I-MIBG-SPECT with or without CT	• Can confirm biochemical diagnosis of Pheo/PGL with 95%–100% specificity	• Lower sensitivity than CT/MRI • 50% of normal adrenal glands demonstrate uptake (false positives) • Sensitivity reduced in familial PGL, malignant disease and extra-adrenal Pheo/PGL
Octreotide scan	• High sensitivity for metastatic disease • Can be positive in tumors that have no MIBG uptake	• Variable uptake in tumors • Less sensitive than 123 I-MIBG for primary disease
18 F-FDG PET/CT	• Superior to 123 I-MIBG, 18 F-FDA in visualization of malignant Pheo/PGL and metastasis; especially in patients with *SDHB* mutations	• Cannot be differentiated between benign and malignant lesions • Expensive
18 F-FDA PET/CT	• Good imaging agent for Pheo/PGL • Superior to 123 or 131 I-MIBG in detection of Pheo/PGL especially for malignant tumors (testing only in VHL)	• Difficult to produce and limited availability • Normal adrenal uptake (false positives) • Expensive
18 F-FDOPA PET/CT	• Superior to 123 I-MIBG in detection of Pheo/PGL • Does not concentrate within normal adrenal tissue	• Low sensitivity for metastatic Pheo/PGL • Limited availability • Expensive
68 Ga-DOTATATE PET/CT	• High sensitivity in patients with high risk of PGL and metastatic disease • Superior to 123-MIBG in detecting lesions in all locations, particularly bone	• Available only in clinical trials • Expensive

Abbreviations: 68-Ga-DOTATATE, 68-gallium 1,4,7,10-teraazacyclododecane-1,4,5,10-teraacetic acid-octreotate; CT, computed tomography; FDA, fluorodopamine; FDG, fluorodeoxyglucose; FDOPA, fluorodihydroxy-phenylalanine; IV, intravenous; MIBG, I-metaiodobenzylguanidine; PGL, paraganglioma; Pheo, pheochromocytoma; SPECT, single-photon emission CT.

Table 3
Genes associated with Pheo/PGL and the associated clinical phenotype and frequency

Gene	Syndrome/Clinical Phenotype	Frequency	Proportion of Malignant Pheo/PGL
FH	Leiomyomas (cutaneous and uterine) and papillary kidney cancer and Pheo/PGL	<1% of all Pheo/PGL patients The % of patients with *FH* who develop Pheo/PGL is unknown	Unknown
HIF2	Multiple paragangliomas and polycythemia	Unknown—Rare	Unknown
MAX	Pheo/PGL	Unknown—Rare	Unknown
NF1	von Recklinghausen disease: peripheral nervous system tumors, gastrointestinal stromal tumors, malignant gliomas, and juvenile chronic myelogenous leukemia	1% of all Pheo/PGL patients 1%–2% of patients with *NF1* develop Pheo/PGL	11% of *NF1* Pheo/PGL are malignant
RET	MEN2A: medullary thyroid carcinoma, pheochromocytoma, primary hyperparathyroidism MEN2B: medullary thyroid carcinoma, pheochromocytoma, mucosal neuromas	5% of all Pheo/PGL patients 50% of MEN2a patients develop Pheo/PGL ~100% of MEN2b patients develop Pheo/PGL	4% of *RET* Pheo/PGL are malignant
SDHA	Pheo/PGL	Unknown—Rare	Unknown
SDHB	Pheo/PGL, renal tumors, familial renal cell carcinoma	10%–15% of all patients with Pheo/PGL The % of patients with *SDHB* who develop Pheo/PGL is unknown	50% of *SDHB* Pheo/PGL are malignant
SDHC	Head and neck PGL, Pheo/PGL	Unknown—Rare	Unknown
SDHD	Head and neck PGL, Pheo/PGL	5%–10% of all patients with Pheo/PGL The % of patients with *SDHD* who develop Pheo/PGL is unknown	Unknown
TMEM127	Pheo/PGL	Unknown—Rare	Unknown
VHL	von Hippel-Lindau disease: retinal and cerebellar hemangioblastoma, renal cell carcinoma, Pheo/PGL, pancreatic neuroendocrine tumors, visceral cysts, Pheo/PGL	5%–10% of all patients with Pheo/PGL 20% of *VHL* patients develop Pheo/PGL	Less frequent than sporadic Pheo/PGL but overall % unknown

Abbreviations: PGL, paraganglioma; Pheo, pheochromocytoma.

Endocrine Neoplasia type 2 syndrome (*RET* proto-oncogene mutation), Von Recklinghausen disease/neurofibromatosis type 1 (*NF-1* mutation), von Hippel-Lindau disease (*VHL* mutation), and familial Pheo/PGL syndrome due to germline mutations of genes encoding succinate dehydrogenase subunits A, B, C, and D (*SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*). In general, these traits are inherited in an autosomal dominant pattern.[5,52] Less frequently, hereditary Pheo/PGLs are associated with familial Pheo syndrome due to germline mutations in *TMEM127* or *MAX*, polycythemia PGL syndrome due to mutations in the *HIF2* gene, or leiomyomatosis and renal cell cancer due to mutations in the fumarate hydratase gene (*FH*).

Most investigators agree that although it is not cost-effective to obtain genetic testing on every patient with a Pheo/PGL, genetic testing should be considered in all patients with Pheo/PGL.[5,18,26,49] It is our practice to routinely refer Pheo/PGL patients to the Hereditary Cancer Clinic for counseling and consideration of genetic testing. There are several reasons to consider testing in all patients. First, as previously stated, it is estimated that a quarter to a third of all patients with Pheo/PGL have disease-causing germline mutations. Second, mutations in the *SDHB* gene have been associated with metastatic disease in approximately 40% to 50% of affected patients.[53,54] Finally, establishing a hereditary syndrome in the proband may result in earlier diagnosis and treatment of Pheo/PGL and other syndromic manifestations in relatives.[26]

There is no consensus to determine who should be tested and for which genes. However, most agree that there should be an algorithm for genetic testing and that it should include factors such as presence of a clinical syndrome, family history, biochemical profile, and/or metastases at presentation.[26,49,51,52,55] Age at presentation, extra-adrenal tumor location, and patients with multiple tumors also should be considered. In a study of 989 nonsyndromic Pheo cases, age younger than 45 years and extra-adrenal tumor location were independently associated with a fivefold increased likelihood of mutation when compared with patients older than 45 years or those with adrenal-based tumors. Furthermore, the presence of multiple tumors was associated with an eightfold increased likelihood of mutation when compared with patients with a single focus of disease.[56] Based on a review of the literature,[26,49,55,56] a proposed algorithm for genetic testing in patients with Pheo/PGL is depicted in **Table 4**. Recently, a genetic sequencing panel was made commercially available that tests for 10 gene mutations: *MAX, MEN1, NF1, RET, SDHAF2, SDHB, SDHC, SDHD, TMEM127*, and *VHL*. As these panels become more available and cost-effective, they will eliminate the need for a stepwise approach to genetic testing and make genetic testing more accessible to all patients with Pheo/PGL.

PREOPERATIVE MANAGEMENT

It is recommended that all patients with functional Pheo/PGL should receive appropriate preoperative medical management to block the effects of catecholamine release during surgical extirpation.[5] The practice of alpha-blockade was first described in the literature in 1956 when Priestly and colleagues[57] reported on a series of 51 Pheos removed without mortality. The lack of mortality was attributed to routine intraoperative use of alpha-blockade.[58] Due to wide-ranging practices and lack of randomized control trials or large prospective cohort studies, there is no consensus and no specific recommendations regarding the preferred drug to be used for preoperative blockade. However, alpha-blockade, calcium channel blockade, or angiotensin receptor blockade have all been named as options. The main goal of preoperative

Table 4
Recommended order of genetic testing by clinical presentation, tumor location and biochemical profile

Clinical Presentation/Biochemical Profile	Gene(s) to Be Analyzed
Syndromic presentation/family history	
VHL	*VHL*
MEN2	*RET*
NF1	*NF1*
Metastatic disease	*SDHB if SDHB negative: SDHD, SDHC, VHL, MAX, FH*
Extra-adrenal	
Dopaminergic	*SDHB, SDHD*
Normetanephrine	*VHL, SDHB, SDHC, SDHD*
Adrenal	
Dopaminergic	*SDHB, SDHD*
Normetanephrine	*VHL, SDHD, SDHB*
Metanephrine	*RET, NF1*
Bilateral or age <45	*VHL, RET*

management of Pheo/PGL is to normalize blood pressure, heart rate, and volume status and prevent a patient from surgically induced catecholamine storm and its consequences on the cardiovascular system.[51]

Nonselective Alpha-Blocking Agent

Phenoxybenzamine is the most recognized and widely used alpha-blocking agent for Pheo/PGL resections. It is a nonselective, irreversible, noncompetitive alpha-blocker. It has a long-lasting effect that diminishes only after de novo alpha-receptor synthesis. The typical starting dosage is 10 mg twice daily. This dosage is increased until clinical manifestations are controlled or side effects appear. Typical side effects include postural hypotension, reflex tachycardia, dizziness, syncope, nasal congestion, and headache. In comparison with selective alpha-blocking agents, phenoxybenzamine is expensive, is not readily available in many pharmacies, and has higher side-effect profile.

Selective Alpha-Blocking Agents

Prazosin, terazosin, and doxazosin have been used as an alternative to phenoxybenzamine. These drugs are short-acting alpha-1 antagonists. They offer the advantage of once-daily dosing and are less expensive and more readily available than phenoxybenzamine. We typically start doxazosin at a dosage of 5 mg daily and the dosage is increased until clinical manifestations are controlled. The most common side effect is orthostatic hypotension. Multiple studies have compared the intraoperative and postoperative hemodynamics as well as outcomes of patients treated with nonselective and selective alpha blockade.[59–63] These studies have demonstrated no difference in the incidence of intraoperative or postoperative adverse outcomes when selective alpha blockade is used as an alternative to nonselective phenoxybenzamine. Thus, the choice between phenoxybenzamine versus selective alpha-blocking agents is at the treating physician's discretion. Dosing frequency, side-effect profiles, availability, and cost should be considered when making this decision.

Beta-Blockers

Patients with catecholamine or alpha-blocker–induced tachyarrhythmia can be treated with beta-blocking agents such as atenolol, metoprolol, or propranolol. Beta-blockers should never be knowingly used without a concurrent alpha-blocker because treatment with only beta blockade may result in unopposed alpha vasoconstriction, which can lead to worsening symptoms of hypertension, end-organ malperfusion, and heart failure.[51]

Calcium Channel Blockers

These agents block norepinephrine-mediated calcium influx into vascular smooth muscle, thereby controlling hypertension and tachyarrhythmias. Calcium channel blockers can be used to supplement alpha blockade in patients with inadequate blood pressure control, can replace alpha blockade in patients unable to tolerate the side effects of alpha-blocking agents, can prevent alpha-blocker–induced sustained hypotension in patients with only intermittent hypertension, and may also prevent catecholamine-associated coronary spasm.[51,64] Nicardipine is typically started at 20 mg 3 times daily and can be increased until symptoms are controlled.

Metyrosine

Metyrosine is a less commonly used agent that blocks catecholamine synthesis by inhibiting the enzyme tyrosine hydroxylase. Metyrosine significantly depletes catecholamine stores, exhibiting its maximum effect 3 days after treatment. The typical starting dosage is 250 mg 4 times daily.[51] Although it is not a first-line agent, it can be used to control high blood pressure refractory to more traditional alpha, beta, or calcium channel blocking agents that can result from extensive metastatic disease.

Fluid Management

Increased preoperative fluid intake is recommended because of the depletion of plasma volume that results from chronic vasoconstriction. Experts recommend salt loading and increased fluid intake before surgery. Small retrospective studies report that initiation of high-sodium diet a few days after the start of alpha blockade reverses blood volume contraction, prevents orthostatic hypotension before surgery, and reduces the risk of significant hypotension after surgery.[26,51,65] Historically, patients were admitted preoperatively for IV fluid administration; to our knowledge, there is no evidence to support the use of IV fluid over increased oral intake in combination with a high-sodium diet, and therefore the additional cost of increased length of hospital stay is not warranted.

There is no gold standard for the duration of preoperative therapy or end points to determine adequate preoperative blockade. Most investigators agree that medical management with the chosen blocking agent should begin at least 7 to 14 days before surgical intervention to allow for adequate time to normalize blood pressure and heart rate. The most commonly used end points that demonstrate appropriate blockade are a normal blood pressure, defined as a systolic blood pressure less than 130 mm Hg seated but greater than 90 mm Hg while standing, and heart rate between 60 and 70 beats per minute sitting and 70 to 80 beats per minute while standing.[5,26,51] Some investigators have advocated that in normotensive patients, preoperative alpha blockade is not essential.[66] However, most providers treating patients with Pheo/PGL agree that some form of preoperative medical management is warranted.

SURGICAL TREATMENT OF THE PRIMARY TUMOR

There are several operative approaches available to the experienced surgeon, including laparoscopic (transperitoneal or retroperitoneoscopic), robotic anterior or posterior, open anterior, lateral flank, or posterior. The choice of surgical approach is determined by patient-related and tumor-related factors. For instance, a smaller Pheo can be removed from a retroperitoneoscopic approach, whereas a larger one (>6 cm) may be resected via the transperitoneal laparoscopic, robotic, or open anterior approach. A large tumor or one suspected to be malignant and/or with involvement of other adjacent organs should be removed using the open approach. Morphometric patient factors also play an important role in the choice of video-assisted posterior versus transperitoneal surgical approach. Very obese patients with a large amount of retroperitoneal fat may not be ideal candidates for a retroperitoneoscopic approach. For most adrenal Pheos, laparoscopic adrenalectomy has become the preferred approach. The benefits of laparoscopic adrenalectomy when compared with open adrenalectomy include decreased operative times, blood loss, duration of hospital stay, and complications.[67–72] Although some recommend an open approach for large lesions (>6 cm),[26] several studies have shown that laparoscopic adrenalectomy is safe and effective for larger pheochromocytomas (>6 cm)[73–75]; yet, larger pheochromocytomas pose unique technical challenges during laparoscopic surgery. Larger tumors result in smaller operative space and therefore make mobilization more difficult. In addition, the increased vascularity and friability displayed by these tumors can make the operation quite challenging and should be approached with caution. Because PGLs are more likely to be malignant and are frequently found in areas difficult for laparoscopic resection, they more commonly require open resection, although some investigators have reported the successful use of laparoscopic approaches for PGL.[76] Details of the technical aspects of each operative approach are beyond the scope of this article.

Surgical management of hereditary Pheo/PGL, particularly patients with VHL and MEN2, often necessitates bilateral adrenalectomy. Bilateral Pheo/PGLs have been shown to develop in approximately 50% of patients with MEN2A and 40% to 60% of patients with VHL.[19,77,78] In patients with synchronous presentation of bilateral tumors, there are 3 options for surgical resection: bilateral total adrenalectomy, cortical sparing adrenalectomy of one adrenal and complete resection of the other, or bilateral cortical sparing procedures on both adrenals. The goal of cortical sparing adrenalectomy is to remove all of the adrenal medulla, leaving behind only cortical tissue, which can prevent the need for chronic steroid replacement and adrenal insufficiency. There is, however, an increased risk of recurrence associated with cortical sparing adrenalectomy.[79] In one study of 91 patients with familial Pheo/PGL, 39 patients underwent bilateral cortical sparing adrenalectomy; acute adrenal insufficiency developed in 3% of patients compared with 20% in the bilateral total adrenalectomy group. The risk of recurrence was 7% in the cortical-sparing group compared with 3% in the bilateral total adrenalectomy group.[79]

The surgical management of malignant Pheo/PGL is not covered in this article. A multidisciplinary team should manage such patients. When possible, the medical management should be optimized and the primary and metastatic tumor burden should be surgically debulked. In a recent large database study of 287 patients with malignant Pheo and 221 patients with malignant PGL, the 5-year overall and disease-specific survival rates were 58.1% and 71.1% for patients with malignant Pheo and 80.0% and 86.4% for patients with malignant PGL.[80] Patients with malignant Pheo/PGL should be considered for enrollment in available clinical trials offering novel treatments.

POSTOPERATIVE MANAGEMENT, OUTCOMES, AND FOLLOW-UP

For most patients who undergo resection of a Pheo/PGL, the postoperative course is uncomplicated. In a recent study of 91 patients who underwent resection of adrenal-based Pheo, the average length of hospital stay was 3 days and the overall complication rate was 10%.[63] Other series report complication rates of 8% to 23% and an average length of hospital stay of 3 to 4 days.[13,81,82] In the current era, 30-day postoperative mortality of Pheo/PGL is less than 5%.[81,82] However, postoperative hypotension due to a combination of the abrupt fall in circulating catecholamines after tumor removal, the continued presence of alpha blockade, preoperative volume contraction, and intraoperative blood loss are not uncommon. The initial treatment for hypotension after extirpation of the Pheo/PGL is volume resuscitation.[14] Patients with persistent hypotension in the setting of volume repletion may require short-term vasopressor support. Approximately 11% of patients have hypotension refractory to volume repletion requiring postoperative vasopressors.[63]

Another well-described postoperative complication associated with resection of Pheo/PGL is hypoglycemia. High levels of preoperative catecholamine can cause suppression of alpha and beta cell function[83] and lead to insulin resistance.[84] Removal of the Pheo/PGL can result in excessive rebound secretion of insulin and hypoglycemia.[85] This occurs in 4% to 17% of patients, typically within the first 4 postoperative hours.[85,86] Therefore, patients should undergo regular glucose monitoring and be placed on dextrose-containing fluids until they are tolerating oral intake. Clinicians should have a low threshold for checking the glucose level if a patient demonstrates symptoms of hypoglycemia postoperatively and initiate dextrose infusion if necessary.[86]

Currently there is no method to rule out potential malignancy or recurrence from a Pheo/PGL. Thus, long-term periodic follow-up is recommended for all cases of Pheo/PGL.[5,51] Most Pheo/PGLs do not recur. The incidence of recurrence is 15% to 17%.[14,87] In one retrospective study of 176 patients with Pheo/PGL diagnosed from 1975 to 2003, the 5-year and 10-year probabilities of recurrence were 6% and 16%, respectively.[87] Due to the risk of recurrence, the National Comprehensive Cancer Network recommends that follow-up consists of history and physical, plasma-free, or urinary fractionated metanephrines and consideration of CT, MRI, or FDG-PET scan at 3 to 12 months after resection, every 6 to 12 months for the first 3 years after resection, and annually from years 4 to 10 after resection.[88] In a review of long-term postoperative follow-up in patients with apparently benign Pheo/PGL, Amar and colleagues[87] agree that patients with sporadic Pheo/PGL less than or equal to 5 cm in size should have clinical follow-up with a history and physical focusing on symptoms of catecholamine excess and blood pressure measurements in addition to plasma-free or urinary fractionated metanephrines 1 year after surgery and then every other year for life. However, they recommend that patients with familial/inherited disease (particularly those with *SDHB* mutations) or with tumors larger than 5 cm should undergo clinical and biochemical follow-up 6 months after surgery and then every year for life because of their increased likelihood of recurrence or malignancy. If a patient is found to have elevated metanephrines he or she should then undergo imaging to localize the recurrent or metastatic disease.[87]

In our practice, patients are seen in clinic at 1 month after resection and undergo measurement of plasma metanephrines. If the patient is asymptomatic and metanephrines are within normal range, the patient is followed in 1 year. Plasma metanephrines are repeated annually with either CT or MRI imaging as first-line modality if abnormalities are noted or suspected. In patients with hereditary Pheo/PGL, the

follow-up may be more frequent and tailored to the likelihood of malignancy and recurrence.

SUMMARY

Pheos and PGLs are well-described yet rare neuroendocrine tumors. The classic clinical signs and symptoms of paroxysmal hypertension, headaches, sweating, and palpitations at presentation are becoming less common as more Pheo/PGLs are being diagnosed incidentally on imaging or by genetic testing. When a Pheo/PGL is suspected clinically, plasma-free metanephrines or urinary fractionated metanephrine levels are highly sensitive in confirming the diagnosis. Genetic testing should be considered for all patients with Pheo/PGL. CT or MRI is often the only imaging modality necessary to localize Pheo/PGL and plan for surgical resection. Selective or nonselective alpha-blocking agents and calcium channel blockers appear to be equally effective in treating the physiologic effects of Pheo/PGL and should be used at the discretion of the treating team before surgical resection. There are several surgical approaches used to remove Pheo/PGL and the choice of approach depends on patient-related and tumor-related factors as well as surgeon preference. Overall, resection of Pheo/PGLs in the current era of preoperative and intraoperative management is well tolerated with low morbidity and mortality. After resection, patients with Pheo/PGL should be followed at least annually with plasma or urine metanephrines with CT or MRI if abnormalities are noted or detected.

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