

PHEOCHROMOCYTOMA AND PARAGANGLIOMA

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ABSTRACT

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumors arising from chromaffin cells of the adrenal medulla or neural crest progenitors located outside of the adrenal gland, respectively. These tumors are derived from either sympathetic tissue in the adrenal or extra-adrenal abdominal locations (sympathetic PPGLs) or from parasympathetic tissue in the thorax or head and neck (parasympathetic PPGLs). The clinical presentation is so variable that a PPGL has been described as "the great masquerader". The varied signs and symptoms of PPGLs are attributed to hemodynamic and metabolic actions of the catecholamines produced and secreted by these tumors. For a better understanding of clinical symptomatology of PPGLs, one needs to be aware of the tumor physiology, biochemistry, and molecular biology, which were discussed in detail in this chapter. While most PPGLs are benign, about 10% of pheochromocytomas and 25% of PGL are malignant. The newer targeted therapies for metastatic PPGLs are likely to be based on our understanding of tumor biology and the design of new highly specific compounds with fewer side effects. There has been an extensive research in the field of PPGLs in the last decade that shed light on genetic etiology and multiple possible metabolic pathways that lead to these tumors. In this article, we detail the current literature on diagnosis and management of PPGLs with a special focus on recent advancements in the field. For complete coverage of this and related areas of endocrinology, please see WWW.ENDOTEXT.ORG.

INTRODUCTION

Pheochromocytomas and paragangliomas (PPGLs) are highly vascular neuroendocrine tumors that arise from chromaffin cells of the adrenal medulla or their neural crest progenitors located outside of the adrenal gland, respectively¹. PPGLs are estimated to occur in about 2–8 of 1 million persons per year and about 0.1% of hypertensive patients harbor a PPGL. About 10% of patients with PPGL present with adrenal incidentaloma². Per 2017 – WHO classification of tumors (fourth edition), based on their location/origin, these neuroendocrine tumors are classified as tumors of the adrenal medulla and extra-adrenal paraganglia³. These tumors are derived either from sympathetic tissue in adrenal or extra-adrenal abdominal locations (sympathetic PPGLs) or from parasympathetic tissue in the thorax or head and neck (parasympathetic PPGLs)⁴. Sympathetic PPGLs frequently produce considerable amounts of catecholamines, and in approximately 80% of patients, they are found in the adrenal medulla^{1,4}. Remaining 20% of these tumors are located outside of the adrenal glands, in the prevertebral and paravertebral sympathetic ganglia of the chest, abdomen, and pelvis. Extra-adrenal PPGLs 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. In contrast, most parasympathetic PPGLs are chromaffin-negative tumors mostly confining to the neck and at the base of the skull region along the glossopharyngeal and vagal nerves, and only 4% of these tumors secrete catecholamines⁴. These head and neck PGLs were formerly known as glomus tumor or carotid body tumors. Most PPGLs represent sporadic tumors and about 35% of PPGLs are of familial origin with about 20 known susceptibility genes making them most strongly hereditary amongst all human tumors^{5,6}. Based on these genetic mutations and pathogenetic pathways, PPGLs can be classified into three broad clusters- cluster 1, cluster 2 and cluster 3. Cluster 1 includes mutations involving in overexpression of vascular endothelial growth factor (VEGF) (due to pseudohypoxia) and impaired DNA methylation leading to increased vascularization. Cluster 2 includes activating mutations of Wnt-signaling pathway (Wnt receptor signaling and Hedgehog signaling). This activation of Wnt and Hedgehog signaling is secondary to somatic mutations of *CSDE1* (Cold shock domain containing E1) and *MAML3* (Mastermind like transcriptional coactivator 3) genes⁷. Abnormal activation of kinase signaling pathways like PI3Kinase/AKT, RAS/RAF/ERK, and mTOR pathways account for cluster 3 mutations^{3,8}. On the other hand, based on biochemical secretory patterns, PPGLs can be characterized into three different phenotypical categories – noradrenergic phenotype (predominant norepinephrine secreting), adrenergic phenotype (predominant epinephrine secreting) and dopamine secreting. These biochemical phenotypes of PPGL lead to a constellation of symptoms (based on the predominant hormone secreted) leading to different clinical manifestations.

CLINICAL FEATURES:

The clinical presentation is so variable that a PPGL has been termed as "the great masquerader". The varied signs and symptoms of PPGLs mainly reflect the hemodynamic and metabolic actions of the catecholamines produced and secreted by the tumors^{5,9}. Although the presence of signs and symptoms of catecholamine excess remains the principal reason for initial suspicion of PPGLs, this does not imply that all PPGLs 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 (based on the biochemical phenotype) from those in whom the tumor is suspected based on signs and symptoms.

Hypertension is the most common sign and may be sustained or paroxysmal, with the latter more usual presentation occurring on a background of normal blood pressure or sustained hypertension. PPGL may also present with hypotension (excessive stimulation of beta adrenoreceptors by elevated levels of epinephrine), postural hypotension or alternating episodes of high and low blood pressure¹⁰. Headache occurs in up to 90% of patients with PPGL. 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 only a few patients can present with flushing¹¹. The presence of 3 Ps triad including headache (pain), palpitations and generalized inappropriate sweating (perspiration) in patients with hypertension should lead to immediate suspicion for a PPGL. Other common (but non-specific) 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. 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, adrenocorticotrophic hormone), intubation, induction of anesthesia, chemotherapy, endoscopy, catheterization, and micturition or bladder distention (with bladder tumors). Less frequent clinical manifestations include fever of unknown origin (hypermetabolic state) and constipation¹². Due to sustained hypertension secondary to α 1- adrenoceptor mediated vasoconstriction, patients with noradrenergic phenotype can have hypertensive encephalopathy sometimes leading to ischemic attack/stroke, intestinal ischemia leading to intestinal necrosis followed by sepsis, renal failure, muscle necrosis and myoglobinuria^{13,14}. In contrary, patients with adrenergic phenotype can present with hypotension resulting in tachycardia and even cardiogenic shock due to the vasodilatory effects of epinephrine, mediated through prominent β 2-adrenoceptor overstimulation^{15,16}. Patients with dopaminergic phenotype may have some very non-specific manifestations as described above in this section, e.g. nausea and vomiting (possibly due to some D2 receptor stimulation in brain), diarrhea (stimulation of D1 receptors in gut) and hypotension (due to vasodilatory effects of dopamine)¹⁷. Except for clinical signs and symptoms as described thus far, patients with malignant PPGL 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 metastases¹⁸.

Highly variable symptomatology in patients with PPGL 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 PPGL with ectopic secretion of corticotrophin or corticotrophin-releasing factor, resulting in the presentation of Cushing's syndrome^{19,20}. PPGLs have also been described that secrete excessive amounts of vasoactive intestinal peptide, this resulting in presentation of watery diarrhea and hypokalemia²¹.

As described above, neglecting the secretory status of these tumors predisposes patients to serious and potentially life threatening cardiovascular complications due to catecholamine excess, including severe hypertension, acute myocardial infarction, cardiac arrhythmias, pulmonary edema, heart failure due to aseptic cardiomyopathy, and shock²².

DIAGNOSIS OF PPGLs:

The diagnosis is based on documentation of catecholamine excess by biochemical testing and localization of the tumor by imaging. Both are of equal importance, although the rule of endocrinology applies to the diagnostic algorithm of PPGL as well, making biochemical diagnosis as initial step followed by localizing studies. Moreover, biochemical analysis helps us in understanding the biochemical phenotype of the tumor so that further genetic and imaging studies can be tailored accordingly.

BIOCHEMICAL TESTING:

Missing a PPGL can have a detrimental outcome. Therefore, biochemical evaluation should include highly sensitive tests to safely exclude a PPGL. PPGLs can secrete all, none, or any

combination of catecholamines (epinephrine, norepinephrine, dopamine) depending upon their biochemical phenotype. As the secretion of catecholamines from a PPGL is episodic; a single estimation of plasma or urinary epinephrine and norepinephrine most likely misses the biochemical diagnosis in about 30% of cases. In contrast, the metabolites of catecholamines (epinephrine is metabolized to metanephrine and norepinephrine is metabolized to normetanephrine) are constantly released into circulation²³. 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 confirmed that measurements of fractionated metanephrine (i.e. normetanephrine and metanephrine measured separately) in urine or plasma provide superior diagnostic sensitivity over measurement of the parent catecholamines²⁴. Consequent to the above considerations, current US Endocrine Society guidelines recommend plasma free metanephrine or urinary fractionated metanephrine as initial screening tests²⁵. These results, in addition to dopamine and plasma 3-methoxytyramine (3-MT as the dopamine metabolite), can be used to accurately establish the biochemical phenotype of a tumor^{26,27}. A high diagnostic sensitivity for the detection of these tumors is achieved if blood measurements are collected in the supine position especially after an overnight fast and after a patient has been recumbent in a quiet room for at least 20 to 30 minutes before sampling²⁸. Fractionated urinary metanephrine, with measurement of urinary creatinine for verification of collection, can be used as alternative options especially in centers where supine blood sampling is not feasible. Caffeine, smoking, and alcohol intake as well as strenuous physical activity should be withheld for approximately 24 hours prior to testing to avoid false-positive results. Certain medications like tricyclic antidepressants, monoamine oxidase inhibitors can cause a false elevation in catecholamine and metanephrine levels¹¹. A detailed list of medications that can interfere with testing is listed in [Table 1](#). One should consider withholding these medications (only if patient's clinical condition permits) that can lead to false-positive test results. A 3-4-fold increase in metanephrine levels above the upper limit of the age-adjusted reference is rarely a false-positive result, except when patients are on antidepressants. Metanephrine levels within the reference range typically exclude the tumors, while equivocal results (<3-4-fold above the upper limit) require additional tests if reference intervals are appropriately established and measurement methods are accurate and precise^{29,30}. False-negative metanephrine could be observed in tumors that are smaller than 1 cm, dopamine-secreting head and neck tumors (recommend measuring 3-MT), or nonfunctional tumors⁵. Also, it is important to note that urine dopamine levels should never be used in the diagnostic work up as most of the dopamine present in mammalian urine is formed in renal cells, rendering this test unacceptable for evaluation of PPGLs²⁷.

As the underlying genetic mutation leads to variable expression of biosynthetic enzymes (due to mutation-dependent differentiation of progenitor cells), there is a profound difference in the types and amount of catecholamines produced by these tumors³¹. Moreover, regulatory and constitutive secretory pathways, which are also genotype dependent, contribute to variations in the catecholamine content displayed by tumors³¹. Hence, greater understanding of the genetic background will allow physicians for further advancements in diagnostic approaches (and thus treatment options). Approaching genetic testing using an individual patients' clinical presentation is considered cost-effective, timely and valuable for early and effective treatment of patients, especially with hereditary PPGLs. For a better understanding of tailoring of biochemical analysis based on the clinical presentation, we briefly describe biochemical phenotype correlations in this section. As described above in the section 1, PPGLs can be broadly classified into three

biochemical phenotypes – noradrenergic, adrenergic and dopaminergic. Tumors can be classified to non-secretory type if they are not making any hormones (usually seen in parasympathetic PPGLs).

Noradrenergic Phenotype:

This phenotype comprises of PPGLs that predominantly produce norepinephrine and are therefore characterized by elevated norepinephrine and normetanephrine levels³². PPGLs of cluster 1 (pseudohypoxia-related tumors) belong to this biochemical phenotype. A typical noradrenergic phenotype is suggestive of mutations in the tumor suppressor von Hippel-Lindau (VHL) in VHL syndrome, succinate dehydrogenase (SDH) type A, B, C, or D, fumarate hydratase (FH), malate dehydrogenase type 2 (MDH2), and endothelial pas domain protein 1 (also known as hypoxia-inducible factor type 2A) (EPAS1/HIF2A) genes. Genetic mutations of SDHAF2 are also included in this cluster though there is limited evidence exists on their biochemical nature (Table 2). Krebs cycle (*SDHx*, *FH*, *MDH2*) and hypoxia signaling pathway (*VHL*, *HIF2A*, *PHD1*, *PHD2*) PGL-related gene mutations cause HIF-2 α stabilization, promoting chromaffin/paraganglionic cell tumorigenesis³³. A summary of the clinical characteristics of patients with each genetic mutation is presented in Table 2. Patients with elevated normetanephrine levels (and/or normal 3-methoxytyramine levels) should undergo genetic screening for mutations in the above-mentioned genes, especially if other syndromic features are absent. The location of PPGLs with the noradrenergic phenotype is typically extra-adrenal; however, they may also be limited only to the adrenal glands, especially in the VHL syndrome. They also often present as multifocal, recurrent, or metastatic.

Adrenergic Phenotype:

PPGLs predominantly secreting metanephrines are included in this phenotype. PPGLs of cluster 2 (kinase signaling-related tumors) belong to this biochemical phenotype. These tumors are usually well differentiated, and contain phenylethanol-N-methyltransferase (PNMT) enzyme that regulates the conversion of norepinephrine to epinephrine. The enzymatic activity is typically located in adrenal medulla and so location of a tumor with this phenotype is typically adrenal, however, they may also be seen in extra-adrenal locations, especially in TMEM127 mutation³⁴. Patients presenting with predominantly elevated levels of metanephrine should usually undergo genetic screening for *RET* and *NF1* mutations first^{5,32}. Nevertheless, most often patients with these mutations are usually first diagnosed based on other syndromic features of the disease and may only require biochemical and genetic testing to confirm the suspicion. Genetic screening for TMEM127 may be considered for adrenergic PPGLs once mutations in *NF1* and *RET* are ruled out³⁵. Other mutation that can be considered under this category is *MAX* mutation, which is intermediate between the adrenergic and noradrenergic phenotype and hence, targeted genetic screening for this gene may be considered in cases of adrenal PPGLs when other susceptibility genes have been ruled out³⁶.

Dopaminergic Phenotype:

PPGLs that predominantly secrete dopamine with or without mild increase in norepinephrine (normetanephrine) are classified under the dopaminergic phenotype. The dopaminergic phenotype is common with head and neck PPGLs (carotid body tumors), though adrenal tumors have also been reported³⁷. The dopamine produced by these tumors is metabolized to 3-MT and so increased 3-MT levels are of an important diagnostic value, especially in cases with normal dopamine levels³⁸. The dopaminergic phenotype is typically seen in metastatic disease,

especially related to *SDHB* and *SDHD* mutations, though there are a few case reports of the dopaminergic phenotype in NF1, VHL, and MEN2A. The common presence of the dopaminergic phenotype in metastatic disease may be attributed to proliferation of poorly differentiated progenitor cells leading to decrease dopamine decarboxylase activity.

LOCALIZATION STUDIES:

Tumor localization should usually only be initiated once the clinical evidence and a biochemical proof of a PPGL is established. In patients with a hereditary predisposition, a previous history of a PPGL, or other PPGL syndromic presentations where the pre-test probability of a PPGL is relatively high, less-compelling biochemical evidence might justify the use of imaging studies. Imaging also plays a key role in a screening process for patients with genetic predispositions to PPGL development. For carrier screening, along with biochemical evaluations, a CT or MRI is often recommended every few years to detect tumors in early stages, if at all. Adding whole-body imaging is particularly important for *SDH* mutation carriers, as these tumors are sometimes missed by only biochemical evaluations³⁹.

Either computed tomography (CT) or magnetic resonance imaging (MRI) are recommended for initial PPGL localization (more than 95% of PPGLs are found)^{1,40}. Compared to MRI, CT has a better spatial resolution and hence used as first choice imaging modality. Though both CT and MRI have equal sensitivity in localizing PPGLs, use of T2-weighted MRI imaging is recommended especially in patients with metastatic PPGL, for detection of skull base and neck PGLs, patients with surgical clips, in patients with an allergy to CT contrast and for patients in whom radiation exposure should be limited (children, pregnant women, patients with known germline mutations, and those with recent excessive radiation exposure).

On CT, adrenal pheochromocytomas typically have a heterogeneous appearance, often with some cystic areas. Depending upon the composition of PPGL, calcifications and/or hemorrhage may be seen. On dual-phase contrast-enhanced CT, pheochromocytomas can also be distinguished from other adrenal masses due to higher intensity during the arterial phase, with enhancement levels greater than 10 HU (usually more than 20 HU is diagnostic) and washout less than 50% at the end of 10 minutes (it is important to note that adrenal cancers also have limited washout)⁴¹. However, in case of high fat content, adrenal pheochromocytoma may also resemble adrenal adenomas. If the adrenal PPGL is less than 3 cm and the patient is younger than 40 years and has no family history of PPGL, no further imaging workup needs to be performed before proceeding to definitive management⁴². On T2-weighted MRI, adrenal pheochromocytoma typically appear as bright lesions (compared to that of liver), although cystic or necrotic components may affect this classic appearance. If imaging of the adrenal glands is normal, imaging of additional areas of the body should be performed. Imaging should be completed of the abdomen, followed by the pelvis, chest, and neck and extremities should be included in case of metastatic disease (to evaluate for bone metastasis).

Although CT and MRI have almost equal and excellent sensitivity for detecting most PPGLs, these anatomical imaging approaches lack the specificity required to unequivocally identify a mass as a PPGL. The higher specificity of functional imaging modalities offers an approach that overcomes the limitations of anatomical imaging, providing justification for the coupling of the two approaches. Upon CT or MRI lesion confirmation, a patient's biochemical phenotype, tumor size, family history, syndromic presentation, and metastatic potential plays a key role to determine the need of functional imaging. The patients with a single, epinephrine or

metanephrine secreting adrenal tumor that is less than 5 cm, will most likely not benefit from additional functional imaging, since these tumors are almost always confined to the adrenal gland and present with a small likelihood of metastases, even if hereditary component is present⁴³. On the contrary, functional imaging is necessary for lesions that secrete norepinephrine or normetanephrine and are larger than 5 cm, or associated with a hereditary tumor syndrome (as these characters determine the metastatic potential). 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 treatment⁴⁴.

Historically, functional imaging has been performed with ¹²³I- or ¹³¹I-metaiodobenzylguanidine (MIBG) scintigraphy. Though ¹²³I-MIBG SPECT has high sensitivity for detection of adrenal pheochromocytoma, it has unacceptably low sensitivity for the detection of extra-adrenal PGLs (56% to 75%) and metastases, especially in the presence of *SDHx* mutations⁴⁵. Moreover, certain medications, such as opioids, tricyclic antidepressants, and anti-hypertensives like labetalol, can also affect MIBG uptake, leading to less intense or false-negative scans. Nonetheless, ¹²³I-MIBG is useful to identify patients with metastatic PPGL because MIBG avid lesions indicate that these patients may benefit from treatment with therapeutic doses of ¹³¹I-MIBG. Given the low sensitivity of MIBG imaging, US Endocrine Society Guidelines recommend using ¹⁸F-FDG PET scan as a preferred modality of functional imaging in patients with metastatic disease²⁵. However, many recent studies have shown that metastatic lesions were missed on ¹⁸F-FDG PET scan^{46,47}. As PPGLs express somatostatin receptors (SSTRs), imaging modalities based on SSTR (DOTA peptides, particularly ⁶⁸GaDOTA(0)-Tyr(3)-octreotate (⁶⁸Ga-DOTATATE) are emerging as gold standard functional tests.

The first functional imaging specific to neuroendocrine tumors, including PPGLs developed was ¹⁸F-fluorodopa (¹⁸F-FDOPA), an amino acid analog and catecholamine precursor that is taken up by the amino acid transporter. Initially lower sensitivity was now improved by inhibiting DOPA decarboxylase by pretreatment with carbidopa, which enhances the tracer uptake by the tumor⁴⁸. From all PPGLs, ¹⁸F-FDOPA PET is extremely sensitive for patients with head and neck PGLs, sometimes identifying small tumors missed by all other imaging techniques. This technique also appears to be particularly effective for patients with *SDH* mutations or biochemically silent PHEO/PGL or both and may be valuable as a screening technique, particularly for patients with *SDHD* mutations. ¹⁸F-fluorodopamine (¹⁸F-FDA), which is similar to dopamine and taken up by norepinephrine transporters. ¹⁸F-FDA PET is another PPGL specific tracer that offers excellent diagnostic sensitivity and spatial resolution, and appears particularly useful for localization of some primary and metastatic PPGLs, but this imaging modality is not used often these days since it has been surpassed by ⁶⁸Ga-DOTATATE and ¹⁸F-FDOPA PET. A prospective study demonstrated the superiority of ⁶⁸Ga-DOTATATE in a cluster of 22 patients, in which DOTATATE could localize 97.6% metastatic lesions whereas ¹⁸F-FDG PET/CT, ¹⁸F-FDOPA PET/CT, ¹⁸F-FDA PET/CT, and CT/MRI showed detection rates of 49.2 %, 74.8 %, 77.7 %, and 81.6 % respectively (p<0.01)⁴⁹. King et al⁵⁰ and recently Janssen et al⁴⁶ reported that ¹⁸F-FDOPA as well as ⁶⁸Ga-DOTATATE PET are equally good in the localization of head and neck *SDHx*-related and non-hereditary PPGLs. However, a recent prospective analysis by Archier et al⁵¹ concluded that ⁶⁸Ga-DOTATATE is superior to ¹⁸F-FDOPA in localizing small head and neck PPGLs especially caused by *SDHD* mutation making it a preferred modality of imaging in head and neck PPGLs. On the contrary, the study showed that small adrenal pheochromocytomas (usually seen with MEN2 and NF1 syndromes) are better detected with

^{18}F -FDOPA⁵¹. This might be secondary to high physiological uptake of ^{68}Ga -DOTATATE in adrenal gland, compared to ^{18}F -FDOPA. **Table 3** summarizes the current proposed PET radiopharmaceuticals for PPGL imaging according to genetic background⁵².

MALIGNANT PPGL

While most PPGLs are benign, about 10% of pheochromocytomas and 25% of PGL are malignant. The prediction of malignant behavior of PPGL is not straight-forward and is often challenging. Several markers (Ki-67 index, expression of heat-shock protein 90, activator of transcription3, pS100 staining, increased expression of angiogenesis genes, and N-terminal truncated splice isoform of carboxypeptidase E)⁵³⁻⁵⁷ and a scoring system (pheochromocytoma of adrenal gland scaled score)⁵⁸ were developed, which were later found to have suboptimal correlation to malignant behavior showing that these techniques may not be sufficient for distinguishing between benign and malignant tumors and that larger studies including various hereditary and non-hereditary PPGLs are definitely needed to confirm some initial findings⁵⁹. Having said that, several independent risk factors for metastatic disease were established, including the presence of *SDHB* mutations, extra-adrenal location, size of primary tumor > 5 cm (in *SDHB*-related PPGLs over 3.5 cm), younger age of initial diagnosis of PPGL and elevated 3-MT levels^{18,49,60-63}.

PPGL typically metastasize to lungs, liver, bones, and lymph nodes and patients with metastatic disease suffer from diminished quality of life due to localized pain caused due to metastasis, consequences of catecholamine excess and of course, treatment side effects⁶⁴. Though bone metastases are thought to be less aggressive with a better survival (compared to non-skeletal metastases), they are associated with complications not limiting to bone pain, spinal cord compression, bone fractures, and hypercalcemia⁶⁵. Irrespective of site of metastases, the 5-year overall survival for malignant PPGL is about 60%⁶³.

MANAGEMENT OF PPGLs:

The definitive treatment of PPGL is surgical excision of the tumor. Laparoscopic surgery is commonly the technique of first choice for resection adrenal and extra-adrenal PPGLs when oncologic principles can be followed⁶⁶. 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 PPGL should therefore receive appropriate preoperative medical management to block the effects of released catecholamines²⁵. Hence, it is of utmost importance that preparation of the patient for surgery requires adequate preoperative medical treatment to minimize operative and postoperative complications. Exceptions to this rule include endocrine emergencies like necrotic PPGL leading to severe hypotension, other surgical emergencies⁶⁷ or the tumors that secrete high amounts of dopamine or epinephrine.

Pre-Operative Medical Management (Blockade):

As described above, once diagnosed with PPGL, patients should be placed on antihypertensive medications, preferentially α followed by β -adrenoceptor blockade¹. **Table 4** summarizes the list of available drugs and suggested doses. The first choice should be an α -adrenoceptor blocker. A β -adrenoceptor blocker may be used for preoperative control of arrhythmias, tachycardia or angina. However, loss of β -adrenergic-mediated vasodilatation in a patient with unopposed catecholamine-induced vasoconstriction via α -adrenoceptors can result in

dangerous increases in blood pressure sometimes hypertensive crisis. Therefore, α_2 -adrenoceptor blockers usually should not be employed without first blocking α_1 -adrenergic mediated vasoconstriction. Labetalol (more potent α_1 than α_2 antagonistic activities with $\alpha_1:\alpha_2$ of 1:5) should not be used as the initial therapy because it can result in paradoxical hypertension due to its high affinity to α_2 -adrenoceptors. Phenoxybenzamine, a long-acting α -adrenoceptor blocker is commonly preferred drug in patients who have elevated blood pressures. Short acting α -adrenoceptor blockers like prazosin, terazosin, and doxazosin are used when phenoxybenzamine is not available or when a patient's hypertension is not severe enough to warrant the use of a long-acting α -adrenoceptor blocker⁶⁸. As there is a high chance that these medications can cause orthostatic hypotension, they should be started at night⁶⁸. The doses should be titrated to achieve normo-tension or mild tolerable hypotension. The patients should also be advised to maintain adequate water and salt intake to maintain adequate intravascular volume. Calcium channel blockers (CCBs) can be added if a goal blood pressure control is not achieved with adequate α - and β -adrenoceptor blockade. CCBs can also be used as initial agents of choice in patients who have normo-tension/mild hypertension, and/or who could not tolerate α -blocker due to hypotension (usually seen in PPGLs that secrete dopamine predominantly). Patients with non-secreting head and neck tumors with normal blood pressure may not be placed on pre-procedural blockade⁶⁹.

In patients who did not achieve adequate blood pressure control despite being on optimized doses of α - and β -adrenoceptor blockade, metyrosine (competitive inhibitor of tyrosine hydroxylase) can be added to prevent catecholamine synthesis. Metyrosine acts by decreasing the catecholamine synthesis and its main side effects include depression, anxiety, and sleepiness due to its effects on central nervous system (as it can cause blood brain barrier)⁶⁹.

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. 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 PPGL should be based on administration of phentolamine. It is usually given as an intravenous 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 $\mu\text{g/kg}$ per minute (stop if no results are seen after 10 minutes)⁶⁹.

Certain medications are to be avoided in patients with PPGLs. Effects of some drugs are more obvious due to their mechanism of action, such as dopamine D2 receptor antagonist metoclopramide. More recently, peptide and corticosteroid hormones, including corticotropin, glucagon and glucocorticoids (intravenous) have been shown to have adverse reactions in this patient population. Other classes of drugs contraindicated in patients with PPGL are tricyclic anti-depressants, 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.

1.1 SURGERY:

As described earlier, surgical resection is the treatment of choice. The risks of operative mortality are extremely low if performed by an experienced surgical team including a skilled anesthesiologist to monitor for intra-operative hypertensive crises⁶⁹. Laparoscopic procedure is the preferred technique when feasible and has similar outcomes as open-surgery. Surgery can also be used as a curative treatment for recurrent, or limited metastatic tumors; it can also be used as a debulking technique for patients with extensive metastatic disease to reduce symptoms and imminent complications from tumor size. However, the long-term benefits of debulking procedures for patients with metastatic disease may be limited⁷⁰.

Post-Operative Management:

Although a few patients suffer from hypotension in the immediate post-operative period, most require treatment, 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 posture⁴².

The long-term prognosis of patients after operation for PPGL is excellent, although nearly 50% may remain hypertensive after surgery. Biochemical testing should be repeated after about 14-28 days from surgery to check for remnant disease. Importantly, 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 is recommended for all cases of PPGL^{5,42}.

Radiofrequency Ablation (Rfa), External Beam Radiation And Radiotherapy:

RFA, external radiation and radiotherapy with ¹³¹I-MIBG therapy can be used in patients with metastatic disease in whom surgery may not be feasible. RFA has been successfully used in liver and bone metastases^{71,72}. External beam radiation is a common treatment modality in patients with inoperable head and neck paragangliomas⁷³. Radiation therapy with gamma knife, or cyber knife have begun to replace traditional external-beam radiation for glomus jugulare tumors, owing to their more precise targeting of radiation and increased dose capability⁷⁴. For patients with a positive MIBG uptake, therapy with ¹³¹I MIBG can be a valuable treatment modality. It is important to note that the patients should be taken off medications (labetalol, tricyclic antidepressants, and certain calcium antagonists) that can block MIBG uptake by the tumors. In some patients, radiotherapy targeting somatostatin receptors (DOTA peptides

(DOTATATE, DOTATOC, and DOTANOC), radio labeled with lutetium (^{177}Lu), yttrium (^{90}Y), or indium (^{111}In) has been successfully used and is currently an emerging modality of therapy for metastatic inoperable PPGLs⁷⁵⁻⁷⁸.

Chemotherapy And Molecular Targeted Therapies:

Traditional chemo-therapy with cyclophosphamide, vincristine, and dacarbazine (CVD) has been used most extensively with progressive and widely metastatic PPGLs^{79,80}. CVD chemotherapy is usually well tolerated for long periods, with an increased time between the doses can be tried in patients who develop toxicities. Clinicians using the chemotherapy, should be aware of potentially fatal complications arising from excessive catecholamine release as tumor cells are destroyed (usually within the first 24 hours) and patient should be closely monitored, preferentially in intensive care unit, especially in patients who have extensive disease and high baseline catecholamine levels. Experience with other chemotherapy agents such as temozolomide; streptozotocin with other agents; ifosfamide; cyclophosphamide and methotrexate; cisplatin and 5-fluorouracil is limited to case reports^{81,82}. Molecular targeted therapies such as sunitinib (tyrosine kinase inhibitor) and everolimus (mTOR inhibitor) have been tried with mixed results⁸³⁻⁸⁵. As we gradually progress in understanding the pathophysiology of PPGLs, newer modalities of targeted therapies can be explored (e.g., HIF pathway and mTOR pathway antagonists)^{33,86}.

TAKE HOME POINTS:

1. PPGLs are neural crest-derived tumors, and 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 and Pacak-Zhuang syndromes.
2. Genetic testing 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. PPGLs are tumors that are mainly diagnosed based on the measurement of plasma or urinary metanephrine and 3-MT since 30% of these tumors do not secrete catecholamines.
4. Patients with metastatic disease should undergo appropriate genetic testing based on the biochemical profile and tumor location.
5. Computed tomography (CT) is the first-choice imaging modality. Magnetic resonance imaging (MRI) is recommended in patients with metastatic PPGL, 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 -FDOPA or ^{68}Ga DOTATATE scanning is preferred functional modality in patients with primary solitary or metastatic disease.
7. ^{123}I -MIBG scintigraphy as a functional imaging modality in patients with metastatic PPGL detected by other imaging modalities when radiotherapy using ^{131}I -MIBG is planned.

8. All patients with a hormonally functional PPGL should undergo preoperative blockade with α -adrenoceptor blockers followed by β -adrenoceptor blockade as the first choice to prevent perioperative cardiovascular complications for 7-14 days.
9. Minimally invasive adrenalectomy is recommended for most adrenal PPGLs and open resection for large or invasive PPGLs to ensure complete resection and avoid local recurrence.
10. Multidisciplinary teams at centers with appropriate expertise to ensure favorable outcome should treat all patients with PPGL.

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Table 1: Medications That Interfere With Testing of Fractionated Plasma or Urinary Metanephrines

	Metanephrine	Normetanephrine
Acetaminophen ^a	-	↑↑
α-Methyldopa ^a	-	↑↑
Tricyclic antidepressants	-	↑↑
Mesalamine ^a /sulfasalazine ^a	-	↑↑
Phenoxybenzamine	-	↑
Monoamine oxidase inhibitors ^b	↑↑	↑↑
Sympathomimetics ^b	↑	↑
Cocaine ^b	-	↑↑
Levodopa ^{a,c}	↑	↑

Symbols: ↑↑, clear increase (≥ 3 -fold above the upper limit depending on the dose and duration of administration); ↑, mild increase (< 3 -fold above the upper limit); -, no increase. Adapted from Lenders et al.³

^a Whether these drugs interfere with the measurement or elevate fractionated plasma or urinary metanephrines depends on the assay and should be withdrawn 5 days before testing. Drug interference is not an issue when mass spectrometry-based assays are used.

^b Monoamine oxidase inhibitors, sympathomimetics, and cocaine can increase catecholamines (thereby metanephrines through peripheral conversion).

^c Levodopa elevates dopamine and thereby methoxytyramine (its measured metabolite), which elevates metanephrine and normetanephrine using non-mass spectrometry-based assays.

Adapted from Hannah-Schmouni et al (11) with permission.

Table 2: Genotype-biochemical phenotype correlation of PPGLs

Table 2 Genotype-Biochemical Phenotype Relationship						
Gene	Transmission	Biochemical profile	Most common PPGL locations	Bilateral PHEO	Malignancy	Most common clinical features/tumors
<i>EPAS/HIF2A</i>	Unknown	NE	Multifocal sPGLs	Possible	29%	Somatostatinoma; polycythemia; ocular lesions
<i>FH</i>	AD	NE	Adrenal PPGL sPGL	Possible	3/8 cases reported	Cutaneous and uterine leiomyoma; type 2 papillary RCC
<i>MAX</i>	AD, paternal	Intermediate ^a	Adrenal PPGL	67%	7-25%	Renal oncocytoma
<i>MDH2</i>	AD	NE	sPGL	Unknown	Unknown	Unknown
<i>NF1</i>	AD	EPI	Adrenal PPGL	16%	~12%	Café-au-lait spots; neurofibromas; axillary and inguinal skin freckling; optic gliomas; iris hamartomas; pseudoarthrosis
<i>RET</i>	AD	EPI	Adrenal PPGL	50-80%	<5%	MEN2A: MTC, primary HPT MEN2B: MTC, Marfanoid habitus, mucosal ganglioneuromas
<i>SDHA</i>	AD	NE; NE + DA NS	sPGL HNPGL	Unknown	0-14%	RCC; GIST; pituitary adenoma
<i>SDHAF2</i>	AD, paternal	Unknown ^a	Multifocal HNPGLs	Not reported	Not reported	Not reported
<i>SDHB</i>	AD	NE; NE + DA NS	sPGL	Rare	31-71%	RCC; GIST; pituitary adenoma; pulmonary chondroma
<i>SDHC</i>	AD	NS; DA NE; NE + DA	HNPGL sPGL	Unknown	0-28%	RCC; GIST; pituitary adenoma
<i>SDHD</i>	AD, paternal	NE; NE + DA NS	sPGL HNPGL	Rare	<5%	RCC; GIST; pituitary adenoma; pulmonary chondroma
<i>TMEM127</i>	AD	EPI	Adrenal PPGL	33%	<5%	RCC
<i>VHL</i>	AD	NE	Adrenal PPGL	50%	<5%	Hemangioblastoma; RCC; PNET; ELST

Abbreviations: AD = autosomal dominant; DA = dopamine; ELST = endolymphatic sac tumor; EPI = epinephrine; GIST = gastrointestinal stromal tumor; HNPGL = head and neck paraganglioma; HPT = hyperparathyroidism; MTC = medullary thyroid carcinoma; NE = norepinephrine; NS = nonsecreting; PNET = pancreatic neuroendocrine tumor; PPGL = pheochromocytoma and/or paraganglioma; RCC = renal cell carcinoma; sPGL = sympathetic paraganglioma.

^aPlease refer to the text for additional detail.

Adapted from Gupta et al (5) with permission.

Table 3: Current proposed PET radiopharmaceuticals for PPGL imaging based on genetic background

	Location	Other related tumor conditions	First-choice radiopharmaceutical	Second-choice radiopharmaceutical
<i>SDHB</i>	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	⁶⁸ Ga-DOTA-SSAs	¹⁸ F-FDG
<i>SDHD</i>	Adrenal/extradrenal	GISTs, RCCs, and pituitary adenomas	⁶⁸ Ga-DOTA-SSAs	¹⁸ F-FDG
<i>SDHC</i>	Adrenal/extradrenal	GISTs, RCCs	⁶⁸ Ga-DOTA-SSAs	¹⁸ F-FDG
<i>FH</i>	Adrenal/extradrenal	Skin and uterine leiomyomas, RCCs, uterine leiomyosarcomas and ovarian mucinous cystadenomas	¹⁸ F-FDOPA	⁶⁸ Ga-DOTA-SSAs
<i>VHL</i>	Adrenal/extradrenal	RCCs, CNS hemangioblastomas, pancreatic and testicular tumors	¹⁸ F-FDOPA	⁶⁸ Ga-DOTA-SSAs
<i>EPAS1/HIF2A</i>	Adrenal/extradrenal	Somatostatinomas	¹⁸ F-FDOPA	¹⁸ F-FDG
<i>MEN2</i>	Adrenal	MTC, parathyroid adenomas, or hyperplasia	¹⁸ F-FDOPA	⁶⁸ Ga-DOTA-SSAs
<i>NF1</i>	Adrenal	Neurofibromas, peripheral nerve sheath tumors, and gliomas	¹⁸ F-FDOPA	⁶⁸ Ga-DOTA-SSAs
<i>TMEM127</i>	Adrenal	RCCs	¹⁸ F-FDOPA	⁶⁸ Ga-DOTA-SSAs
<i>MAX</i>	Adrenal/extradrenal	Renal oncocytomas	¹⁸ F-FDOPA	⁶⁸ Ga-DOTA-SSAs

Adapted from Taïeb et al (52) with permission.

Table 4: Medications used for symptom management and preoperative blockade for PPGLs

Medications used for symptom management and preprocedural blockade.

Drug	Classifications	Doses	Recommended use
α-Blockers			
Phenoxybenzamine (Dibenzyline)	Long lasting, irreversible, and noncompetitive	10 mg 1-3 times daily	First choice for α-adrenoceptor blockade
Prazosin (Minipress)	Short-acting, specific, and competitive	2-5 mg 2-3 times daily	<ul style="list-style-type: none">• When phenoxybenzamine is not available• For patients who cannot tolerate phenoxybenzamine• For patients with mild hypertension
Terazosin (Hytrin)	Short-acting, specific, and competitive	2-5 mg/d	
Doxazosin (Cardura)	Short-acting, specific, and competitive	2-8 mg/d	
β-Blockers			
Atenolol (Tenormin)	Cardioselective	12.5-25 mg 2-3 times daily	To control tachyarrhythmia caused by catecholamines or alpha-blockade
Metoprolol (Lopressor)	Cardioselective	25-50 mg 3-4 times daily	
Propranolol (Inderal)	Nonselective	20-80 mg 1-3 times daily	
Calcium channel blockers			
Amlodipine (Norvasc)	Extended-release action	10-20 mg/d	<ul style="list-style-type: none">• To provide additional blood pressure control for patients on alpha blockers• For patients who cannot tolerate alpha blockers• For patients with intermittent hypertension
Nicardipine (Cardene)		60-90 mg/d	
Nifedipine (Adalat)		30-90 mg/d	
Verapamil (Covera-HS and Calan-SR)		180-540 mg/d	
Catecholamine synthesis inhibitors			
Metyrosine (Demser)		250 mg every 8-12 h for a total dose of 1.5-2 g/d	To provide additional blood pressure control for patients on adrenoceptor blockade

Adapted from Martucci et al (42) with permission.