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Review Article

Diagnosis and Management of Pheochromocytomas and Paragangliomas:

A Guide for the Clinician

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Agenda:

- Introduction
- Clinical presentation and Evaluation
- Diagnostic workup
- Imaging
- Association with Genetic syndromes
- Treatment
- Pathology
- Surveillance

Introduction

- Pheochromocytomas and paragangliomas (PPGLs) are unique neuroendocrine tumors.
- The World Health Organization (WHO) defines paragangliomas (PGLs) as nonepithelial neuroendocrine neoplasms, which can produce and secrete catecholamines into circulation.
- PGLs can be parasympathetic or sympathetic.
- Pheochromocytomas (PCCs), originating from the chromaffin cells of the adrenal medulla, are sympathetic, and the WHO classifies them as intra-adrenal PGLs.

Introduction

- PPGL are rare with an overall incidence of around 0.66 cases per 100,000 people per year.
- PCC account for ~80% of PPGL.
- PPGL are not to be referred to as benign and malignant, but are rather localized or metastatic, and the WHO considers all PPGL to have metastatic potential.
- About 10 to 25% of PPGL become metastatic, spreading to nonchromaffin tissue sites, including bones and lymph nodes, with no curative options.
- This review describes the significant advancesin diagnostic testing, imaging, and management.

Clinical presentation and Evaluation

- Most PPGL are found incidentally.
- Those identified through workup of symptoms tend to be larger and associated with higher levels of catecholamines than those discovered incidentally or through screening in people with associated hereditary conditions.
- Sporadic cases usually are detected in the 4th to 5th decade of life, whereas most hereditary PPGL present at younger ages.

Clinical presentation and Evaluation

- PPGL are considered secretory when secreting high levels of catecholamines/metanephrines into the circulation and nonsecretory when these levels are measured to be normal.
- However, it is important to note that nonsecretory PPGL may still arise from sympathetic ganglia and make and store catecholamines with the potential to release the hormones anytime, including during tumor manipulation intraoperatively.

Clinical presentation and Evaluation

- Therefore, peri-operative a-adrenergic blockade should be considered for all PPGL, except for nonsecretory head and neck PGL (HNPGL), because they are derived from parasympathetic ganglia.

Clinical presentation and Evaluation

Sympathetic PPGL :

- Sympathetic PPGL (sPPGL) make and typically secrete high levels of catecholamines which stimulate the sympathetic nervous system via a- and b-adrenergic receptors.
- This causes vasoconstriction, increases peripheral vascular resistance, and causes a rise in blood pressure, often at the expense of volume depletion; hence, patients can present with orthostasis as well. Paroxysmal hypertension, palpitations, syncope, anxiety, and hyperglycemia are more commonly seen in epinephrine-secreting PCC, whereas headaches, sweating, and persistent hypertension are more often seen in norepinephrinesecreting PPGL, although there is a significant crossover (Table 1).

Table 1
Clinical Symptoms, Signs, and Consequences of PPGL

Due to catecholamine excess levels	Due to location and size
• Asymptomatic • Hypertension (persistent, paroxysmal) • Headaches • Diaphoresis • Palpitations/tachycardia/ arrhythmia • Nausea/vomiting • Constipation • Flushing • Weight loss • Orthostatic hypotension/ Syncope • Hyperglycemia • Anxiety • Tremors • Weakness • Myocardial infarction • Stroke • Cardiomyopathy/myocarditis • Impaired renal function • Catecholamine crisis/ multiorgan failure	Head and neck: • Asymptomatic • Tinnitus • Hearing loss • Headache • Horner syndrome • Dysphagia • Voice change Chest: • Asymptomatic • Chest pain Abdomen: • Asymptomatic • Abdominal pain • Constipation • Swelling • Hematuria Pelvis: • Asymptomatic • Hematuria • Swelling • Headache or spells with micturition or bowel movement

Abbreviations: PPGL = pheochromocytomas and paragangliomas.

Clinical presentation and Evaluation

- Rarely, pure dopamine-secreting tumors can present with hypotension.
- Up to half of the patients with secreting PPGL have evidence of hyperglycemia (pre-diabetes or diabetes), which remits in more than three fourths of patients postoperatively.
- sPPGL can also cause symptoms based on the specific location (eg, bladder PGL presenting with hematuria or spells occurring with micturition).

Clinical presentation and Evaluation

- People with sPPGL can present with a catecholamine crisis, with or without a precipitating cause, leading to severe hemodynamic instability and even multiple end organ damage.
- Catecholamine crisis should be considered in cases of unexplained shock, left ventricular failure, multiple organ failure, and sepsis-like picture with negative cultures.

Clinical presentation and Evaluation

- Some patients present with takotsubo cardiomyopathy, a catecholamine-induced cardiomyopathy characterized by severe left ventricular dysfunction from arterial vasoconstriction and vasospasm in the absence of significant obstructive coronary artery disease.

Clinical presentation and Evaluation

Parasympathetic PGL :

- PGL that form from the parasympathetic nervous system are often found incidentally or during workup for symptoms related to mass effect.
- They can be found anywhere in the body with most in the head, neck, and thorax.
- Typical symptoms of HNPGL include headaches and cranial nerve abnormalities, which can be severe, including tinnitus, dysphagia, pain, and hearing loss (Table 1).
- About 4% of HNPGL can be secreting.

Diagnostic workup

Biochemical Testing :

- Screening for sPPGL should be considered for patients with uncontrolled or early onset hypertension, episodes potentially secondary to catecholamine excess, and for a mass in a likely PPGL location.
- Those with HNPGL should also be screened biochemically, not because the HNPGL is likely to be secreting, but because they may have another primary PPGL that will need treatment before surgical resection of the HNPGL.
- Finally, those with a prior history of PPGL or a known genetic predisposition should be screened with biochemical evaluation at least annually.

Diagnostic workup

Biochemical Testing :

- Plasma-free metanephrines or 24-hour urine fractionated metanephrines are recommended for screening.
- Some studies suggest that plasma methoxytyramine may be useful when concerned with metastatic disease.
- Plasma tests are more convenient than 24-hour urine collections.
- Diagnostic performance is similar for patients with low suspicion of disease, whereas plasma measurements are superior for high-risk patients due to the slightly higher sensitivity.

Diagnostic workup

Biochemical Testing :

- The negative predictive value of these tests is high; however, false positive results are not uncommon, often from medications and other substances (Table 2).
- Patients should avoid caffeine, nicotine, and alcohol on the day of the testing.
- Plasma-free metanephrines can be falsely elevated in chronic renal failure stage 3.

Table 2

Medications Causing False Elevation of Metanephrines/Catecholamines

Medications
Dopamine-containing medications (ie, ropinirole, cabergoline, etc.)
Tricyclic antidepressants
Cocaine
α-Adrenergic blockers, phenoxybenzamine
Monoamine oxidase inhibitors
Sympathomimetics (amphetamines, ephedrine, and albuterol)
Sulfasalazine
Buspirone
Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors (SSRI/SNRI)

Diagnostic workup

Biochemical Testing :

- Metanephrine or normetanephrine levels at least two-fold above the upper limit of the normal reference range indicate a high probability of PPGL.
- Elevation less than two-fold is indeterminate and should be repeated.
- If an interfering medication can be safely stopped, consider holding for at least three half-lives (typically 5-14 days).

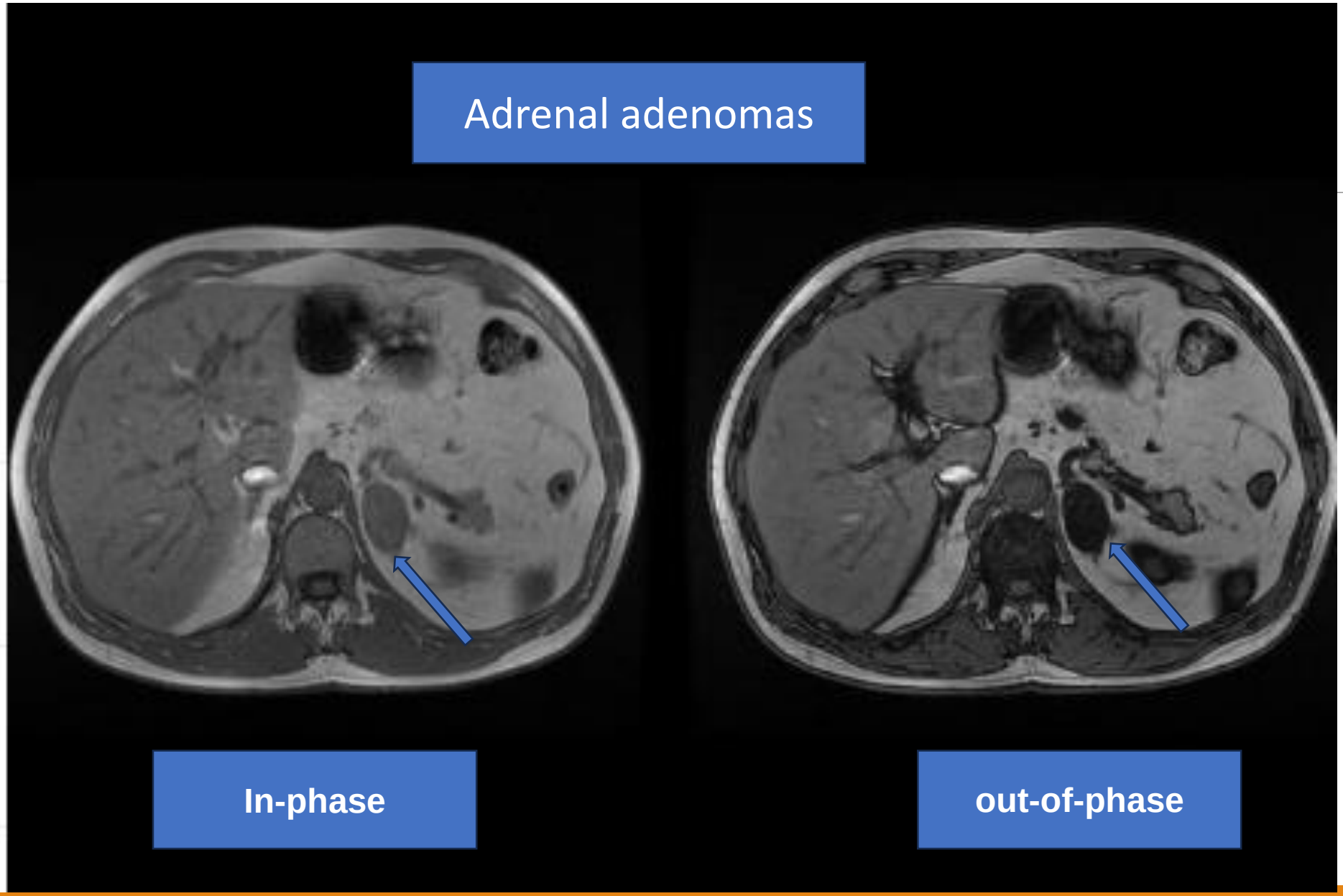
Diagnostic workup

- Guidelines suggest that plasma metanephrines should be drawn with the patient in the supine position for at least 30 minutes with an indwelling catheter.
- This is not always feasible in a busy clinical laboratory.
- Practically, if the test results drawn while sitting up are negative, this is reassuring.
- If there are indeterminate results, and interfering medications have been ruled out, we suggest repeating supine or performing 24 hour urine tests.
- If there is true elevation greater than two-fold upper limit of the normal reference range, then it should be followed by imaging to localize the tumor.

Imaging

- After biochemical confirmation, cross-sectional imaging with CT or MRI is the next step.
- PPGLs often appear as a heterogeneous mass and may be associated with calcifications, vascularity, or necrosis. Almost all PCC on unenhanced CT scans have HU > 10 (99%).
- On MRI, 90% of adrenal adenomas show loss of signal in the “out of phase” sequence, whereas most PCC do not. PPGL also show a hyperintense signal (“light bulb sign”) on T2-weighted images.
- In general, MRI is more helpful for evaluating HNPGL and when avoiding excessive radiation (eg, children, pregnant women, people with PPGL susceptibility gene pathogenic variants [PVs] who will have lifelong imaging, etc.).

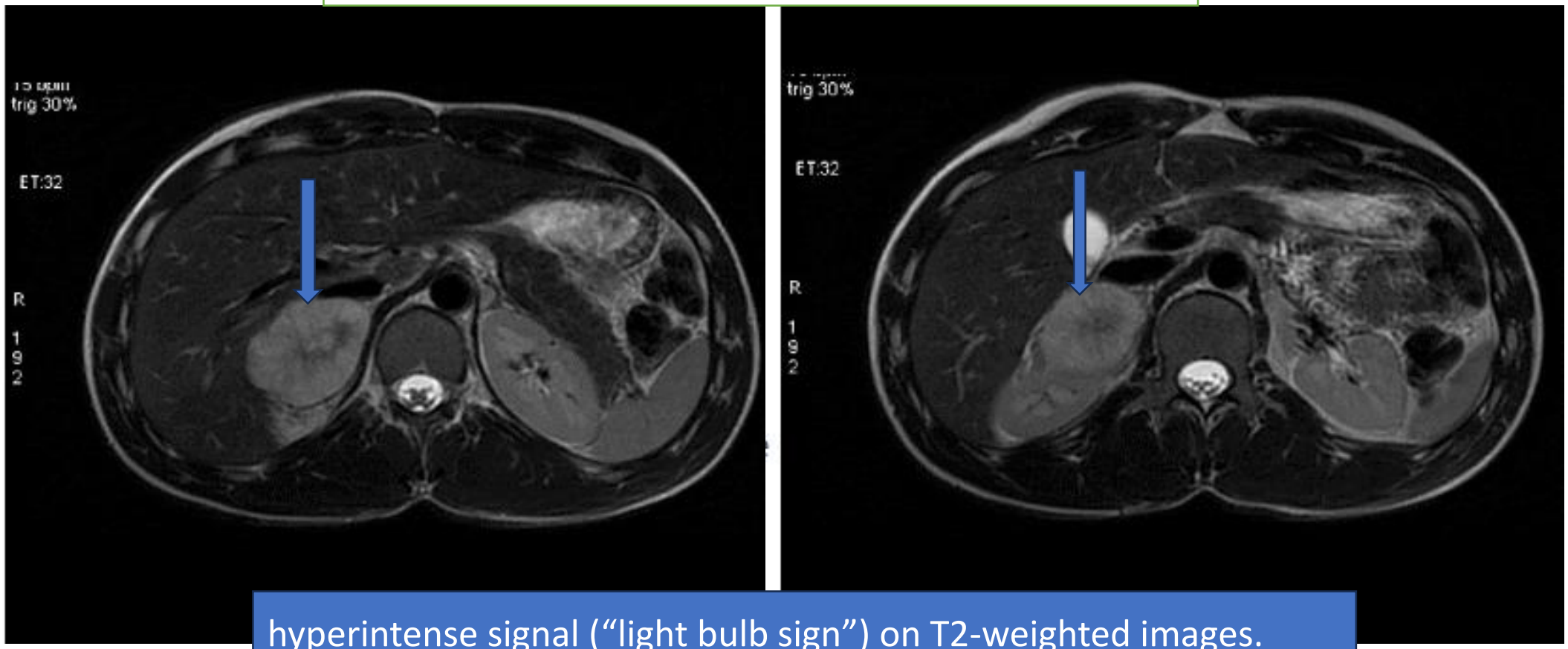
Adrenal adenomas



In-phase

out-of-phase

Adrenal pheochromocytoma



hyperintense signal (“light bulb sign”) on T2-weighted images.

Imaging

- Functional imaging with nuclear medicine scans can be helpful under certain circumstances.
- The cost of these scans in the United States is high and not always covered by insurance; therefore, they are not routinely used as the first step for imaging.
- However, they have great utility when concerned with metastatic disease or choosing potential radionuclide therapy for the treatment of unresectable or metastatic PPGL (mPPGL).

Imaging

- A systematic review and meta-analysis of radionuclide imaging showed that the sensitivity and specificity for PPGL are highest using gallium-68-DOTATATE positron emission tomography/computed tomography ([68Ga] -DOTATATE PET/CT).
- Dihydroxy-[18F] fluorophenylalanine (18FDOPA PET/CT) demonstrated the second highest sensitivity (80%) but is not widely available in most centers outside of a research basis.
- 18F-FDG PET/CT is less sensitive (74%) and less specific for PPGL.
- I-123-MIBG (iodine meta-iodobenzylguanidine) scans are the least sensitive for detecting PPGL.

Association with Genetic syndromes

- PPGL have the highest hereditary component of all human solid tumors, with up to 30 to 40% of patients (and 80% of pediatric patients) having a germline PV in a known susceptibility gene.
- More than 12 well-defined susceptibility genes and several other gene associations have been identified (Table 3).
- Nearly half of the inherited PPGL have PVs in the SDHx genes, with SDHB being the most common.

Association with Genetic syndromes

Table 3
PPGL Susceptibility Genes

Gene	Genetic syndrome	Prevalence of PVs in PCC/PGL	Clinical features
SDHA	Hereditary paraganglioma pheochromocytoma syndrome	<1-3%	• PCC, PGL (penetrance ~10% by age 70) • High risk of metastatic PPGL (~12%) • GIST
SDHB	Hereditary paraganglioma pheochromocytoma syndrome	9-10%	• PCC, PGL (penetrance ~25% by age 60) • High risk of metastatic PPGL (~25-50%) • RCC and GIST
SDHC	Hereditary paraganglioma pheochromocytoma syndrome	1%	• PCC, PGL (often HNPGL and thoracic) • Unknown risk of metastatic PPGL • RCC and GIST
SDHD	Hereditary paraganglioma pheochromocytoma syndrome	2-9%	• PCC, PGL (penetrance ~43% by age 60) • HNPGL common • High risk of multifocal primary PPGL • Lower risk of metastatic PPGL (<5%) • RCC and GIST • Paternal inheritance
SDHAF2	Hereditary paraganglioma pheochromocytoma syndrome	<0.1-0.1%	• HNPGL (can be bilateral) • Paternal inheritance
VHL	Von Hippel-Lindau	4-7%	• PCC>>PGL, (penetrance ~20%) • PCC often bilateral • Low risk of metastatic PPGL • CNS hemangioblastoma • RCC and renal cysts • Endolymphatic sac tumors • Pancreatic neuroendocrine tumors and pancreatic cysts

Association with Genetic syndromes

RET	Multiple endocrine neoplasia 2	6%	MEN2A • PCC (penetrance ~50%) • PCC often bilateral • Low risk of metastatic PPGL • Medullary thyroid cancer • Primary hyperparathyroidism MEN2B • PCC (penetrance ~50%) • PCC often bilateral • Low risk of metastatic PPGL • Medullary thyroid cancer • Ganglioneuromas • Mucocutaneous neuromas • Marfanoid body habitus
NF1	Neurofibromatosis type 1	3%	• PCC (penetrance low ~1-7%) • PCC often bilateral • High risk of metastatic PPGL (~12%) • Neurofibromas (cutaneous or plexiform) • Cafe au lait macules • Axillary/inguinal freckling • Iris hamartomas (Lisch nodules) • Optic gliomas • Bony lesions
MAX		0.8-1%	• PCC > PGL • May be at a higher risk of multifocal and metastatic disease • Possible paternal inheritance
TMEM127		0.6-2.1%	• PCC > PGL • Risks for multifocal disease • RCC
FH	Hereditary leiomyomatosis and renal cell carcinoma syndrome	<1%	• RCC • Uterine leiomyomas • Skin leiomyomas • PCC, PGL (penetrance very low, rare)
EPAS1		<1%	• Polycythemia • Somatostatinoma • PGL > PCC • Somatic mosaicism

Abbreviations: GIST = gastrointestinal stromal tumor; HNPGL = head and neck paragangliomas; PCC = pheochromocytomas; PGL = paragangliomas; RCC = renal cell carcinoma.

Association with Genetic syndromes

- Each susceptibility gene has its unique set of characteristics in terms of penetrance, propensity to develop metastatic disease, and other associated conditions and tumors, as detailed in Table 3.
- Of patients with metastatic PPGL, about 40 to 45% have an SDHB PV, about 50% have sporadic disease (no known germline PV), and the remainder have PVs in the other susceptibility genes.

Association with Genetic syndromes

- Detection of PVs guides the management of not only the proband but also of any affected family members.
- Importantly, the absence of a personal or family history of PPGL does not rule out a hereditary component given the low penetrance for most genes and paternal inheritance for some genes.
- Therefore, clinical genetic testing should be offered to all patients with PPGL by referral to hereditary cancer genetics clinics or as ordered by the physician through commercial companies.

Association with Genetic syndromes

- Once a susceptibility gene PV is identified, gene-specific guidelines direct screening and surveillance for PPGL and other related manifestations.
- Active screening improves outcomes, as has been shown for SDHB carriers by detecting tumors at smaller sizes, reducing risks of metastasis, and reducing mortality rate as compared to the index case.

Treatment

Surgery :

- Surgery is the mainstay for the treatment of primary PPGL and should be offered whenever feasible, except for some skull-based PGL when significant morbidity may occur due to cranial nerve damage. In these cases, active observation and/or radiation may be appropriate.
- For non-HNPGL, minimally invasive approaches (laparoscopic or retroperitoneal) are generally recommended, but an open approach is recommended for large (>6 cm) or invasive tumors to ensure complete resection, prevent tumor rupture, and avoid local recurrence.

Treatment

Surgery :

- Cortical-sparing adrenalectomy should be considered to preserve adrenal function in those with known genetic syndromes presenting with higher risks of bilateral PCC (eg, MEN2 and VHL). After cortical-sparing adrenalectomy, significant recurrence rates are less than 5%.
- This decision and risk of recurrence should be measured against the risk of adrenal crisis in those with bilateral adrenalectomy left with primary adrenal insufficiency.
- In patients with mPPGL, surgical resection of the primary tumor is recommended if the tumor is secreting, if removal will help prevent complications from local compression, or if systemic therapy can be offered and primary tumor resection can help decrease tumor burden.

Treatment

Perioperative Medical Management:

- Perioperative medical management has the following 2 important aspects:
  (a) prevention of hypertensive crisis and tachycardia intraoperatively and
  (b) prevention of hypotension and bradycardia postoperatively.

- Thus, it is critically important to identify a surgeon and anesthesiologist experienced with PPGL. Most experts suggest α -adrenergic blockade be done before resection.

Treatment

Perioperative Medical Management:

- Nonsecreting sPPGL can still make and store hormones that can be released when the tumor is manipulated during surgery.
- Hence, α-adrenergic blockade should be strongly considered.
- On the other hand, nonsecreting HNPGL may not need medical preparation because these are typically from the parasympathetic chain and likely are not storing hormones.

Table 4
Oral Perioperative Medical Therapies

Classes	Names	Starting dosage range	Maximum dosage range	Side effects
Nonselective noncompetitive α-adrenergic blocker	Phenoxybenzamine	10 mg every 12 h	10-40 mg every 8 h	Orthostasis, reflex tachycardia, nasal stuffiness
Selective competitive α-adrenergic blockers	Doxazosin	1-2 mg daily	4-24 mg every 12 h	Orthostasis, reflex tachycardia, nasal stuffiness
	Prazosin	1-2 mg daily	5 mg every 8 h	
Nonselective β-adrenergic blockers	Propranolol	20 mg every 12 h	20-80 mg every 8-12 h	Bradycardia, fatigue, dizziness, asthma, exacerbation
Selective β-adrenergic blockers	Metoprolol tartrate	25 mg every 12 h	50-100 mg every 12 h	
	Atenolol	25 mg daily	25-100 mg daily	
Combined α- and β-adrenergic blockers	Labetalol	100 mg every 12 h	1200 mg every 12 h	Hypertension if used before α-adrenergic blockade is achieved. Fatigue, dizziness
	Carvedilol	6.25 mg every 12 h	25 mg every 12 h	Hypertension if used before α-adrenergic blockade is achieved. Fatigue, dizziness
Calcium channel blockers	Amlodipine	5 mg daily	10 mg daily	Peripheral edema
	Nifedipine	30 mg every 12 h	60 mg every 12 h	Peripheral edema, headache
Tyrosine hydroxylase inhibitor	Metyrosine	250 mg every 12 h, dose increased over 3-7 d as follows: 250 mg every 6 h followed by 500 mg every 6 h followed by 750 mg every 6 h	750 mg every 6 h	Nausea, upset stomach, headache, dizziness, drowsiness, depression, galactorrhea, extrapyramidal symptoms, crystalluria

Table 5
Intravenous Perioperative and Intraoperative Medical Therapies

Classes	Names	Purpose	Dosage range	Onset of action
Intravenous saline infusion	Normal Saline 0.9%	Started preoperatively and continued intraoperative and postoperatively for volume expansion to prevent postoperative hypotension	The rate should be based on the intravascular volume status, and comorbidities like congestive heart failure, renal failure, etc.	Few min
α-Adrenergic blocker	Phentolamine	Antihypertensives (contraindicated in patients with coronary artery disease)	Bolus: 2.5-5 mg at 1 mg/min, repeated every 3-5 min Continuous: 100 mg in 500 mL of 5% dextrose 20-100 mg/h	1-2 min
α-Adrenergic blocker and 5-HT1A blocker	Urapidil	Antihypertensives (can be administered to patients with coronary artery disease)	Bolus: initial dose 25-50 mg bolus Continuous: 10-15 mg/h	1-5 min
β-Adrenergic blocker	Esmolol	Antihypertensives as well as atrioventricular nodal blocking agents for tachyarrhythmias	Bolus: 500 mcg/kg in 1 min, repeat bolus after 5 min (if needed) Continuous: 25-100 mcg/kg/min, increase infusion rate to 300 mcg/kg/min (if needed)	1-5 min
Calcium channel blockers	Nicardipine	Antihypertensives	Starting dose: 5 mg/h, increased by 2.5 mg/h every 5 min (if needed), maximum dose 15 mg/h	2-4 min
	Clevidipine	Antihypertensives (contraindicated in patients with soybean or egg allergies, deficiencies in lipid metabolism)	Starting dose: 1-2 mg/h, increase by doubling the dose every 90 s (if needed), maximum dose 32 mg/h	2-4 min
Arterial and venous vasodilator	Sodium nitroprusside	Antihypertensives (can induce intracoronary steal)	Starting dose: 0.5-1.5 mcg/kg/min, dosage range: 0.5-4 mcg/kg/min	Immediate
Venous vasodilator	Nitroglycerine	Antihypertensives (beneficial in patients with ischemic heart disease)	Infusion adjusted according to the response within the range of 10-200 mcg/min	2-5 min
Miscellaneous α-adrenergic blocker Inhibits catecholamine release	Magnesium sulfate	Antihypertensive, inhibits catecholamines release, antiarrhythmic	Loading dose: 40-60 mg/kg followed by infusion of 1-4 g/h	immediate

Treatment

- A systematic review and meta-analysis of 1344 patients in 11 studies compared patients treated with noncompetitive nonselective vs competitive selective a-adrenergic blockade and concluded that there was a higher intraoperative maximum blood pressure and more frequent intraoperative use of vasodilators among patients treated with selective α -adrenergic blockade, but the risks of both postoperative hypotension (95% CI: 9.38 to 4.21, P ¼.46) and overall morbidity (OR: 0.99, 95% CI: 0.67-1.45, P ¼.94) were comparable.

Treatment

- Furthermore, the prospective Pheochromocytoma Randomized Study Comparing Adrenoreceptor Inhibiting Agents for Preoperative Treatment trial randomized 144 patients to pretreatment with either phenoxybenzamine or doxazosin at unusually high doses (maximum daily dosage of phenoxybenzamine 140 mg or doxazosin 48 mg). They found that the phenoxybenzamine group had a lower peak systolic blood pressure and less need for vasodilating drugs.

Treatment

- however, there were no difference postoperatively regarding the occurrence of hypotension (40.0% vs 38.8%, P >.99) or use of vasoconstrictive/inotropic drugs (33.3% vs 32.4%, P >.99), and no difference in the rate of cardiovascular complications. Because of the comparable efficacy, higher cost, and lower availability of phenoxybenzamine, the competitive selective α-adrenergic blockers (ie, doxazosin and prazosin) have become the mainstay.

Treatment

- Practically speaking, patients should start on the low-dose α -adrenergic blockade and the dose titrated up based on the hemodynamic response with the goal BP<110 to 120/80. Typical blockades take about 10 to 14 days to avoid side effects from rapid titration of medications.

Treatment

- Mild tachycardia and/or orthostasis can be a sign of adequate α -adrenergic blockade; however, this can also be a sign of hypovolemia, for which those with PPGL are at high risk, and this can increase the risk of postoperative hypotension.
- Therefore, once patients have lower BP and/or tachycardia, patients should be advised to expand volume by liberal salt and fluid intake while paying close attention to their cardiac status.

Treatment

- At this point, β -adrenergic blockers can be added if needed to control expected reflex tachycardia.
- Initiating β -adrenergic blockade before achieving α -adrenergic blockade can cause theoretical hypertension because of unopposed α -adrenergic action.
- Resting heart rate in the 70 to 80 bpm range is desired to prevent tachyarrhythmias intraoperatively.

Treatment

- Labetalol provides higher β-adrenergic blockade than α -adrenergic blockade and, therefore, should not be used as initial therapy but can be added after α -adrenergic blockade.
- Calcium channel blockers inhibit noradrenaline-mediated calcium influx into vascular smooth muscles and are helpful as a second-line agent.
- In addition, angiotensin converting enzyme inhibitors and angiotensin receptor blockers can also be added if needed after α -adrenergic blockade if BP is not at goal (especially useful in those with underlying cardiovascular disease).

Treatment

- Metyrosine, a tyrosine kinase inhibitor, can be an effective addition to the conventional regimen to improve intraoperative hemodynamics, but given the cost and side effects, it is generally only used in those with known recent cardiovascular events who are at high risk for hemodynamic swings intraoperatively.

The last dose of all antihypertensives should be administered on the morning of the planned tumor resection.

Treatment

- Perioperative blockades can be challenging in patients who are normotensive.
- Ensuring good hydration and salt intake early can allow for the α -adrenergic blocker to be titrated up.
- Calcium channel blockers can be particularly helpful in these cases, given the lower risk of hypotension.

Treatment

- In retrospective studies, less than half of patients had postoperative hemodynamic instability, and when it occurred, only one third showed persistent instability lasting more than 6 hours.
- Hypoglycemia is a rare potential postoperative complication. Patients should be monitored closely for a few hours postoperatively and then most can be safely transitioned to the floor.

Pathology

- Pathologic scoring systems are not very useful to predict the prognosis or development of metastatic disease.
- The Pheochromocytoma of the Adrenal gland Scaled Score (PASS) which is based on histologic criteria has significant inter- and intraobserver variation.
- The Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) score is based on histologic criteria along with some more objective markers such as the Ki-67 index and biochemical secretion.

Pathology

- The WHO and other expert consensus guidelines support the use of the TNM staging system in the American Joint Committee on Cancer 8th Edition for pheochromocytoma and extraadrenal sPPGL (Table 6).
- Although not perfectly accounting for the uniqueness of PPGL, it is a starting point to help advance continuity and cancer staging.

Table 6
American Joint Committee on Cancer 8th Staging System for Pheochromocytoma/Paraganglioma*,†

Stage	Definition
I	T1N0M0
II	T2N0M0
III	T1-2N1M0 OR T3 Any N M0
IV	Any T Any N M1
Definition of tumor origin (T) TX Primary tumor cannot be assessed T1 PCC size <5 cm in greatest dimension, no extraadrenal invasion T2 PCC size ≥5 cm, sympathetic PGL of any size, no extraadrenal invasion T3 Tumor of any size with invasion of surrounding tissues (eg, liver, pancreas, spleen, and kidneys)	
Definition of regional lymph node (N) NX Regional lymph nodes cannot be assessed N0 No lymph node metastasis N1 Lymph node positive	
Definition of distant metastasis (M) M0 No distant metastasis M1 Distant metastasis M1a Distant metastasis to only bone M1b Distant metastasis to only lymph nodes/liver or lung M1c Distant metastasis to bone plus multiple other sites	

* Parasympathetic paraganglioma (eg, head and neck PGL) are not staged (as per AJCC 8th edition).
† Table adapted from Amin et al AJCC Cancer Staging Manual.[69]

Unresectable and/or Metastatic PPGL

- All PPGL have the potential to metastasize, and approximately 10% to 20% of patients will develop metastases even many years after initial diagnosis.
- Therefore, long-term follow-up is necessary for all patients.
- There are no good predictors for metastasis but several factors may increase risks such as a large tumor size (>5 cm for PCC and >4 cm for PGL), gross large vessel invasion, extraadrenal location, SDHB PVs, younger age at presentation, persistently elevated catecholamine levels postoperatively, and possibly high Ki-67 or mitotic index.

Unresectable and/or Metastatic PPGL

- In patients with mPPGL, the clinical course is highly variable with some patients having rapid progression and some more indolent courses.
- A retrospective review of 272 patients with mPPGL found that the factors associated with rapid disease progression and shorter disease-specific survival are male sex, older age, larger tumor size, elevated plasma dopamine, methoxytyram extensive metastatic burden, extraadrenal tumor location, SDHB PV, and not performing surgery of primary tumor.

Unresectable and/or Metastatic PPGL

- All patients with secreting mPPGL should be treated for a long term with α -adrenergic blockers, including before initiation of any systemic or locoregional ablative treatment to prevent catecholamine-induced crisis from the tumor lysis reaction.
- Additional treatment modalities, such as stereotactic radiotherapy, cytotoxic chemotherapy, targeted agents, and I-131-MIBG or 177Lu- DOTATATE as well as clinical trials, can be considered with the aim to control both the tumor growth as well as the hormone secretion as discussed in guidelines and outside the scope of this review.
- Treatment with bone-specific therapy agents such as zoledronic acid or denosumab should also be used in the setting of oligometastatic or widely metastatic bony metastases.

Surveillance

- All patients who have had PPGL should be monitored lifelong with biochemical testing 3 to 8 weeks after initial surgery and then every 6 to 12 months based on the presence of high-risk features discussed above.
- Surveillance with imaging is typically only performed for those with high-risk disease or nonsecreting primary PGL.
- In addition, even for those with nonsecreting PGL, biochemical testing should be done at least annually to detect any additional primary PPGL.
- Patients who have had VHL, RET, or NF1-associated PPGL should have at least annual biochemical testing with plasmafree metanephrines.

Surveillance

- Patients who have had other hereditary PPGL, such as SDHx-associated PPGL, are recommended to have at least annual biochemical testing and full body imaging from the skull base to pelvis at least every 2 to 3 years if not more often depending on patient and tumor characteristics.
- In patients with mPPGL, biochemical evaluation and anatomical imaging should be considered every 3 to 6 months in the first year, and if the disease is stable then the interval can be extended to every 6 to 12 months.

Pediatric PPGL

- PPGL are very rare tumors in childhood with up to 80% being hereditary and with VHL and SDHB/D PVs most commonly seen in the pediatric population.
- Just as for adults, all pediatric patients with PPGL should undergo clinical genetic testing and lifelong screening and surveillance because over half will develop additional primary tumors and/or metastatic disease throughout their lifetime.
- Because of the paucity of data, the management of PPGL in children is based on the data and experience of adult patients and should be managed by an expert multidisciplinary team.

Pregnancy and PPGL

- A multicenter retrospective study and systematic review of the literature included 232 patients with PPGL who had a total of 249 pregnancies and showed that PPGL diagnosis was made before pregnancy in only 15% of patients, during pregnancy in 54%, and after delivery in 31% of cases.
- Lack of timely diagnosis and treatment led to 27-fold higher risks of severe maternal or fetal complications, including death from hypertensive crisis and other cardiovascular complications due to catecholamine excess.

Pregnancy and PPGL

- In patients who were diagnosed before or during pregnancy, treatment with α -adrenergic blockers helped prevent adverse outcomes (OR 3.6; 95% CI: 1.1-13.2);
- However, antepartum surgery did not improve outcomes (no surgery vs surgery: OR 0.9; 95% CI: 0.3- 3.9).
- Sixty-six percent of patients who underwent genetic testing showed a positive result for a known susceptibility gene PV.

Pregnancy and PPGL

- Therefore, in women of reproductive age with known genetic predisposition, counseling about biochemical testing and screening before conception is recommended and testing for secreting PPGL during pregnancy if not done immediately prior is also recommended.
- MRI without contrast is the imaging of choice during pregnancy and any pregnant woman with sympathetic PPGL should be treated with α -adrenergic blockade.

Conclusion

- PPGL are unique tumors that must be considered in the differential diagnosis to be diagnosed.
- Even then, diagnosis can be challenging; however, more sensitive and specific diagnostic tests are available now for both biochemical testing and imaging.
- Once diagnosed, all patients should be referred for clinical genetic testing, given up to 40% are hereditary.
- All patients with PPGL need lifelong follow-up, given the potential long latency for recurrence or metastatic disease.
- Future studies focus on understanding tumorigenesis and metastatic potential and identifying better predictive and prognostic markers.