PHEOCHROMOCYTOMA

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Definition & Terminology

PHEOCHROMOCYTOMA

A catecholamine-secreting neuroendocrine tumour arising from chromaffin cells of the adrenal medulla. The term is derived from Greek: **phios (dusky) + chroma (colour) + kytos (cell)**, reflecting the dark staining of the tumour with chromium salts.

Pheochromocytoma	Paraganglioma (PGL)	PPGL (Umbrella Term)
Arises from adrenal medulla chromaffin cells	Arises from extra-adrenal sympathetic or parasympathetic ganglia	Pheochromocytoma + Paraganglioma collectively

Epidemiology & Key Facts

0.1–0.6%	2–8/milion	35–45 yrs	~40%
of HTN patients have PPGL	annual incidence (population)	peak age at diagnosis	hereditary (germline mutation)

- **Distribution: ~80% adrenal (pheo), ~20% extra-adrenal (PGL).**
- **"Rule of 10" (now outdated but historically taught):**
  - 10% bilateral, 10% extra-adrenal, 10% malignant, 10% familial — these rates are now recognised to be significantly higher.
- Malignancy: Defined by metastasis (not histology). ~15–17% overall; higher with SDHB mutations (up to 70%)

- Adrenal incidentaloma: 5% of incidentally found adrenal masses are PPGLs

Clinical Presentation: The Classic Triad & Beyond

Classic Triad (in <50% of cases):

- 😟 Episodic Headache
- 💧 Diaphoresis (Sweating)
- 💓 Palpitations / Tachycardia

Hypertensive patterns:

- Sustained hypertension (~50%)
- Paroxysmal hypertension (~45%)
- Hypertensive crises / urgencies
- Orthostatic hypotension (β2 effect)
- Normotension in ~5% (silent tumours)

Other features:

- Weight loss, pallor, anxiety
- Hyperglycaemia / new-onset DM
- Dilated cardiomyopathy (Takotsubo-like)
- Constipation / ileus
- Incidentally found adrenal mass
- Triggered by: anaesthesia, contrast, beta-blockers, TCA, tyramine

Biochemical Investigations: First-Line

Plasma free metanephrines (metadrenaline + normetadrenaline) are the TEST OF CHOICE

Test	Sensitiviy	Specificiy	When to Use
Plasma free metanephrines	97–99%	82–96%	First-line; best for high-risk/hereditary
24h urinary fractionated metanephrines	96–97%	85–95%	First-line alternative; good for intermittent secretion
24h urinary catecholamines	84–91%	88–95%	Adjunct; not recommended as sole test
Plasma catecholamines	~85%	~80%	Useful during symptomatic episode
Chromogranin A	~80%	~70%	Useful in non-functional PGL; affected by PPIs

- Interpretation: **>4× ULN = highly likely PPGL; 1–4× ULN = borderline** .
- False positives: medications (TCAs, levodopa, methyldopa, decongestants), stress, renal failure, sleep apnoea
- Clonidine suppression test: used for borderline plasma normetanephrine; failure to suppress (>40%) is diagnostic

Imaging Investigations

Imaging is performed ONLY after biochemical confirmation — never first-line

Modality	Sensitivity	Specificity	Best For	Notes
CT Abdomen/Pelvis (with contrast)	88–100%	70–80%	First anatomic imaging; adrenal pheo	Risk of hypertensive crisis — alpha-block first
MRI Abdomen (T2-weighted)	93–100%	50–90%	Pregnant patients, contrast allergy, PGL	Hyperintense on T2; no radiation
^{123}I-MIBG Scintigraphy	77–90%	95–100%	Functional imaging; staging	Requires thyroid protection; avoid contrast 2 wks prior
^{68}Ga-DOTATATE PET/CT	93–100%	~100%	Metastatic/hereditary PPGL, head/neck PGL	Preferred over MIBG; superior resolution
^{18}F-FDG PET/CT	74–100%	~95%	SDHB-mutated, malignant PPGL	High metabolic activity in aggressive tumours

Preoperative Medical Management

GOAL: Block catecholamine effects and restore haemodynamic stability before surgery

Step 1	Step 2	Step 3
Alpha-Blockade (FIRST & mandatory) Phenoxybenzamine (non-competitive, irreversible) Start 10 mg BD → titrate Prazosin used now. Duration: minimum 10–14 days pre-op Target: BP <130/80 mmHg	**Beta-Blockade (ONLY after alpha-block)** Add propranolol or atenolol if tachycardia/arrhythmia NEVER start beta-blocker alone — risk of hypertensive crisis (unopposed alpha stimulation) Target HR: 60–80 bpm	**Volume Expansion & Diet** High-salt diet + liberal fluid intake - Counteracts catecholamine-induced volume contraction. Reduces post-op hypotension risk.

Surgical Management

Surgical resection is the only curative treatment for PPGL

- **Preferred approach: Laparoscopic adrenalectomy**
  - Gold standard for unilateral adrenal pheo ≤6 cm; shorter hospital stay, less morbidity
- **Open adrenalectomy:**
  - Large tumours (>6 cm), invasive tumours, prior abdominal surgery
- **Cortical-sparing (partial) adrenalectomy:**
  - Bilateral pheo (hereditary syndromes like VHL, MEN2) — to avoid lifelong steroid dependence
- **Paraganglioma resection:**
  - Approach determined by location — retroperitoneal, thoracoscopic, or open approach
- **Intraoperative hazards:**
  - Catecholamine surge on tumour manipulation.
  - Post-resection hypotension — IV fluid bolus, phenylephrine (alpha-agonist preferred)

Malignant PPGL: Diagnosis & Management

Malignancy = presence of metastases (lymph node, bone, liver, lung) — no histological criteria exist

Risk factors for malignancy:

- **SDHB germline mutation (strongest predictor)**
- **Extra-adrenal location**
- **Large tumour size (>5 cm)**
- **Dopaminergic biochemical phenotype**
- **Ki-67 index >3% on histology**
- **PASS/GAPP score (histopathological scoring)**

Treatment options:

- Surgical debulking — if feasible
- ^{131}I-MIBG therapy — for MIBG-avid tumours; Azedra (high-activity MIBG) FDA-approved
- ^{177}Lu-DOTATATE (PRRT) — for somatostatin receptor-positive tumours
- Chemotherapy — CVD regimen (cyclophosphamide, vincristine, dacarbazine)
- Targeted therapies — sunitinib (anti-VEGFR); trials with **cabozantinib**, olaparib (SDHB)
- **MDT approach mandatory — endocrinology, nuclear medicine, oncology**

5-year survival: ~50% for malignant PPGL; better outcomes with early detection and MIBG therapy

PPGL & Chronic Kidney Disease

Renal manifestations of catecholamine excess:

- Hypertensive nephrosclerosis — sustained or episodic severe HTN → glomerular injury, arteriosclerosis
- Reduced RBF — vasoconstriction reduces renal perfusion; may present as acute kidney injury
- Rhabdomyolysis-associated AKI — rarely due to catecholamine-induced muscle ischaemia
- Haemolytic uraemic syndrome-like presentation — catecholamine-induced microangiopathy (case reports)
- Proteinuria — secondary to hypertensive glomerular damage or catecholamine-mediated podocyte injury

Diagnostic challenges in CKD:

- Metanephrines are renally cleared → accumulate in CKD. GFR <30 may cause values 2–3× ULN without PPGL
- 24h urine collection unreliable in CKD — incomplete collections, variable tubular handling
- Strategy: Use plasma free metanephrines (less affected than urine); values >3–4× ULN still diagnostically significant
- Clonidine suppression test has reduced utility in CKD — interpret with caution
- Functional imaging (^{68}Ga-DOTATATE PET) can help clarify when biochemistry is equivocal

Diagnostic Algorithm for Suspected PPGL