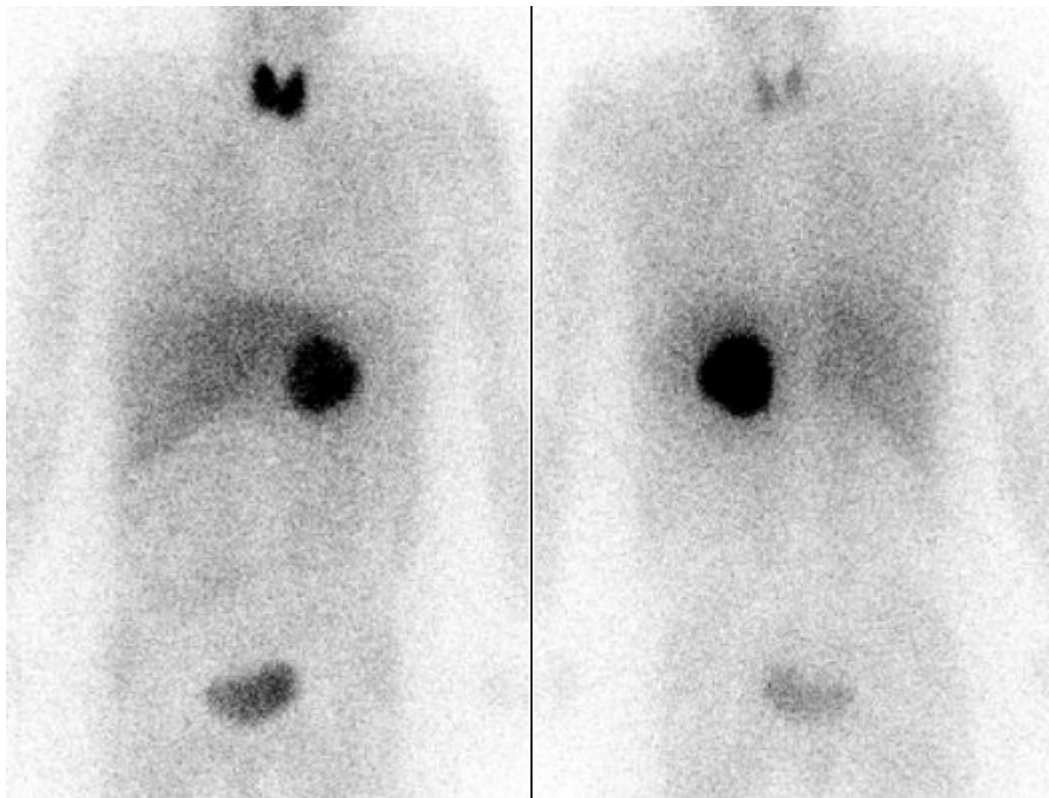


Pheochromocytoma (PCC) — Diagnosis and Surgery

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There are two types of catecholamine secreting tumors: pheochromocytomas which arise from the chromaffin cells of the adrenal medulla and paragangliomas which arise from the sympathetic ganglia or other cells derived from the neural crest. Catecholamines include epinephrine and norepinephrine, and both are released upon the stimulation of the sympathetic preganglionic nerve fibers during times of stress or sympathetic activation.



Overview

Most of the **norepinephrine secretion** into the blood is from sympathetic neuronal innervation to the blood vessels. The secretion of epinephrine and norepinephrine is responsible for many physiological actions that help the body adapt to stress.

Catecholamines increase blood glucose level through activation of **lipolysis** and **gluconeogenesis**. They increase blood pressure, heart rate, and cardiac contractility. Catecholamine secreting tumors can be sporadic or familial associated with other disorders e.g. **multiple endocrine neoplasia syndrome II (MEN II)**, **Von Hippel Lindau syndrome** and **neurofibromatosis type I (NF I)**.

About **10%** of the catecholamine secreting tumors are multiple neoplasms, 10% are bilateral and 10% arise from extra-adrenal sites, while 90% are from the adrenal medulla. 10% are benign and 90% are malignant with local and distant spread to other organs.

The average diameter is about **6 cm**, especially for sporadic tumors. Malignant tumors are usually large in size with capsule invasion and/or distant metastasis. Coexistence of parathyroid tumors and medullary thyroid carcinoma is part of **MEN II** syndrome. Paragangliomas can also arise on both sides of the aorta, carotid artery and along nerve pathways.

Clinical Picture of Pheochromocytoma

Patients with the familial disease will have varying presentations according to other comorbidities. Less than 50% of patients will complain of **hypertension** or **tachycardia** which are the most common complaints. Measurement of circulating catecholamines will be within a normal range. The release of catecholamine usually follows abdominal compression, anesthesia, postural changes or emotional stress.

Episodic release of catecholamines into the circulation leads to paroxysmal attacks of headache, palpitation, sweating, postural hypotension, cold skin, angina, nausea, vomiting, dyspnea, and vision abnormalities. Some patients present with secondary or resistant hypertension, impaired glucose tolerance, tremors, cardiomyopathy or panic-like attacks.

Diagnosis of Pheochromocytoma

The diagnosis of hormone-secreting tumors depends on both **hormonal measurement** and **imaging studies**. Measurement of 24-hour urinary metanephrines and catecholamines is the initial test of choice. Metanephrines are the breakdown products of catecholamines which are excreted in the urine.

Epinephrine and norepinephrine are metabolized into free and sulfate conjugated metanephrines. Metanephrines levels in normal blood are extremely low.

Elevated levels of catecholamines and metanephrines are highly suggestive of pheochromocytoma with a sensitivity that is close to 100%. The next step is the measurement of plasma fractionated metanephrines and plasma catecholamines.

Presence of **adrenal mass** is not conclusive for the diagnosis of pheochromocytoma. The diagnosis should be confirmed with elevated catecholamine levels. **Incidentaloma** is non-functioning tumors that are discovered accidentally on imaging studies or clinical exam without causing symptoms.

Indications for hormonal testing: Typical clinical presentation of tachycardia, sweating and headache, patients with familiar MEN II syndrome, NF II or Von Hippel Lindau syndrome, patients with early-onset hypertension before 20 years or resistant hypertension, patients with idiopathic cardiomyopathy, adrenal mass on radiography and atypical type II diabetes mellitus in a young slim person.

CT & MRI are sensitive and specific imaging studies for adrenal tumors, especially sporadic pheochromocytoma which is usually more than 3 cm in diameter.

Iodine metaiodobenzylguanidine scintigraphy (MIBG): radioactive iodine taken by adrenergic tissues similar to norepinephrine so it is useful with a large adrenal mass or

suspicious of multiple paraganglionic small tumors. Genetic testing should be performed in patients with familiar pheochromocytoma or associated familial syndromes.

Venous sampling is not reliable as catecholamine levels will be higher than normal with false-positive results. A guided biopsy also should be avoided due to the high risk of complications.

Staging of Pheochromocytoma

- **Localized tumor:** The tumor is localized to one or both adrenal glands and to one side only in case of paraganglioma.
- **Regional tumor:** The tumor has spread to the regional lymph nodes and/or regional tissues.
- **Metastatic tumor:** The tumor has spread to distant organs including the liver, lung, brain, and bones.

Management of Patients with Pheochromocytoma

Genetic counseling is the first step to know other risk factors or familial syndromes associated with the disease. Indications for genetic testing include a **positive family history** of familial pheochromocytoma syndrome, diagnosis made before the age of 40, **bilateral disease** or **malignant tumor**. Genetic testing is recommended also for family members of patients with a confirmed diagnosis and positive genetic mutations.

Symptomatic treatment is indicated for patients with a confirmed diagnosis of pheochromocytoma and complaining of symptoms of hypertension, headache, and palpitations.

Medications that control the heart rate and blood pressure include beta and alpha-blockers respectively. Combination of **alpha-blockers**; phenoxybenzamine or doxazosin and **beta-blockers**; propranolol, is the best treatment regimen to control blood pressure and heart rate before surgery. These medications should be used for 3 weeks before surgery. The alpha blockade should proceed with beta blockade to prevent unopposed alpha-receptors stimulation and severe hypertension.

During surgery, **Nitroprusside infusion** is used for emergency elevation in the blood pressure. Hypotension following bilateral adrenalectomy is managed with **norepinephrine infusion** and **hydrocortisone injection**. Hydrocortisone is also helpful after bilateral adrenalectomy to avoid adrenal insufficiency.

Surgical adrenalectomy is the definitive treatment of choice. The adrenal gland is removed with the local lymph nodes, followed by measurement of the catecholamines level to check if there is still elevation of the hormones. **Lifelong hormonal replacement** is indicated in the case of bilateral adrenalectomy.

Surgical treatment according to the stage

A localized tumor is treated with **unilateral total adrenalectomy**. A regional tumor is removed with other organs that the tumor has spread to, including the kidneys, lymph nodes, part of the liver and blood vessels. A metastatic tumor is treated with **palliative surgery** to improve the quality of life.

Other treatment options include **tumor ablation, arterial embolization, radiation therapy** and **chemotherapy**. Targeted therapy using **tyrosine kinase inhibitor**,

Sunitinib, is used for recurrent and metastatic pheochromocytoma. A familial tumor is treated with **selective tumor removal** from both glands to avoid total bilateral adrenalectomy and lifelong hormonal replacement.

Follow-up with measurement of catecholamines in the blood and urine. A CT scan, MRI and MIBG are necessary to exclude a recurrent tumor and determine treatment plans.

References

Merck manual, Pheochromocytoma

[Pheochromocytoma and Paraganglioma Treatment \(PDQ®\)-Patient Version](#) via National Cancer Institute, Cancer.gov

[Clinical presentation and diagnosis of pheochromocytoma](#) via uptodate.com

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