Chapter 12
Pheochromocytoma/Paraganglioma: Update on Diagnosis and Management

Ivana Jochmanova and Karel Pacak

Abbreviations

^{18}F-DOPA	^{18}F-Dihydroxyphenylalanine
^{18}F-FDA	6-^{18}F-Fluorodopamine
^{18}F-FDG	^{18}F-Fluorodeoxyglucose
3PO	3-(3-Pyridinyl)-1-(4-pyridinyl)-2-propen-1-on
^{68}Ga-DOTATATE	^{68}Ga-DOTA(0)-Tyr(3)-octreotate
Acetyl-CoA	Acetyl coenzyme A
ACLY	ATP citrate lyase
AD	Autosomal dominant
AM	Morning
AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
ATRX	Alpha thalassemia/mental retardation syndrome X-linked
BCH	2-Aminobicyclo(2,2,1)-heptane-2-carboxylic acid
BP	Blood pressure
BPTES	Bis-2-[5-phenylacetamido-1, 2, 4-thiadiazol-2-yl] ethyl sulfide

I. Jochmanova, M.D., M.Ed
Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, 1E-3140, 10 Center Drive, MSC-1109, Bethesda, MD 20892-1109, USA

1st Department of Internal Medicine, Medical Faculty of P.J. Šafárik University in Košice, Trieda SNP 1, 04011 Košice, Slovakia
e-mail: ivana.jochmanova@nih.gov

K. Pacak, M.D., Ph.D., D.Sc (✉)
Section on Medical Neuroendocrinology, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, 1E-3140, 10 Center Drive, MSC-1109, Bethesda, MD 20892-1109, USA
e-mail: karel@mail.nih.gov

A.C. Levine (ed.), *Adrenal Disorders*, Contemporary Endocrinology,
DOI 10.1007/978-3-319-62470-9_12

CHC	α-Cyano-4-hydroxycinnamate
CT	Computed tomography
CVD	Cyclophosphamide, vincristine, dacarbazine
E	Epinephrine
EBRT	External beam radiation therapy
EGCG	Epigallocatechin gallate
EGLN1/2	Egl-9 family hypoxia-inducible factor 1/2 (see also *PHD2/1*)
FH	Fumarate hydratase
GDH1	Glutamate dehydrogenase 1
GLUT	Glucose transporter
GOT2	Glutamate oxaloacetate transaminase 2
GPNA	γ-L-Glutamyl-p-nitroanilide
GPT2	Glutamate pyruvate transaminase 2
HIF	Hypoxia-inducible factor
HIF2A	Hypoxia-inducible factor 2 alpha
HK	Hexokinase
HNPGL	Head and neck paraganglioma
HPLC	High-performance liquid chromatography
HR	Heart rate
HRAS	Harvey rat sarcoma viral oncogene homolog
IDH	Isocitrate dehydrogenase
KIF1Bβ	Kinesin family member 1B
LAT1	L-type amino acid transporter 1
LDHA	Lactate dehydrogenase A
MAX	myc-associated factor X gene
MCT	Monocarboxylase transporter
MDH2	Malate dehydrogenase 2
MEN2A/2B	Multiple endocrine neoplasia, type 2A/2B
MIBG	Metaiodobenzylguanidine
MN	Metanephrine
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MTY	Methoxytyramine
NE	Norepinephrine
NF1	Neurofibromatosis type 1
NF1	Neurofibromin 1
NMN	Normetanephrine
NS	Nonsecreting
PDH	Pyruvate dehydrogenase
PET	Positron emission tomography
PFK	Phosphofructokinase
PGC1α	Peroxisome proliferator-activated receptor-γ coactivator 1α
PGL	Paraganglioma
PHD1/2	HIF prolyl hydroxylase domain-containing protein 1/2 (see also *EGLN2/1*)

PHEO	Pheochromocytoma
PI	Paternal inheritance
PKM2	Pyruvate kinase, isoenzyme 2
RECIST	Response evaluation criteria in solid tumors
RET	Rearranged during transfection proto-oncogene
RFA	Radio-frequency ablation
ROS	Reactive oxygen species
SDH	Succinate dehydrogenase
SDHA, SDHB, SDHC, SDHD	Succinate dehydrogenase subunits A, B, C, and D
SDHAF2	SDH assembly factor 2
TAPGL	Thoracic and abdominal paraganglioma
TMEM127	Transmembrane protein 127
VEGF	Vascular endothelial growth factor
VHL	von Hippel-Lindau

Introduction

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine, catecholamine-producing tumors arising from adrenal medulla or extra-adrenal sympathetic and parasympathetic ganglia, respectively [1]. PHEOs/PGLs are mostly benign tumors, but metastatic disease is not rare, especially in patients with specific genetic backgrounds [2–4]. Although well known since the early twentieth century, PHEO/PGL diagnosis and treatment can still be a very challenging task. In up to 50% of patients, these tumors are not recognized [5]. Recently, research has brought new information about the pathophysiology of PHEO and PGL and enabled the development of new methods for diagnosis of these tumors as well as potential new treatment options.

Clinical Presentation of Pheochromocytoma and Paraganglioma

Deciphering the signs and symptoms of patients with a certain disease poses one of the most challenging parts of the diagnostic process. Comprehensive personal and family history and clinical examination are therefore the key components for the diagnostic process. Patients harboring PHEOs/PGLs exhibit a variety of nonspecific symptoms (Table 12.1) resulting from hemodynamic and metabolic actions of circulating catecholamines, or other amines and neuropeptides, secreted by the tumor [7, 10, 11]. Stimulation of α-adrenoceptors leads to an increase in systemic vasoconstriction and peripheral pressure and a decrease of perfusion in target organs (heart, brain, kidneys, gastrointestinal tract). Activation of β-adrenoceptors results in inotropic and chronotropic effects on myocardium and the release of renin [12].

Table 12.1 Clinical signs and symptoms exhibited by patients with PHEO/PGL

Symptoms	Frequency	Signs	Frequency
Headache	++++	Hypertension	++++
Palpitations	+++	– Sustained	++
Sweating	+++	– Paroxysmal	++
Anxiety/nervousness	++	Tachycardia or reflex bradycardia	+++
Abdominal/chest pain	++	Sweating/diaphoresis	+++
Nausea	++	Orthostatic hypotension	+++
Tremulousness	++	Pallor	++
Fatigue/weakness	++	Fever/hypermetabolism	++
Dyspnea	+	Hyperglycemia	++
Dizziness/faintness	+	Vomiting	++
Heat intolerance	+	Weight loss	++
Pain/paresthesias	+	Increased respiratory rate	++
Visual symptoms	+	Flushing	+
Constipation	+	Convulsions	+
Diarrhea	+	Psychosis (rare)	+

Frequency: up to 25%, +; 26–50%, ++; 51–75%, +++; 76–100%, ++++ [6–9]

Patients with primarily epinephrine-secreting PHEOs/PGLs more frequently display signs and symptoms compared to those with norepinephrine-producing tumors. Patients with dopamine-secreting PHEOs/PGLs usually present with less typical symptoms, such as hypotension, diarrhea, and weight loss. However, the severity of symptoms does not necessarily correlate with plasma catecholamine levels [7]. Clinical symptoms can mimic a number of different conditions (Table 12.2) and they vary from patient to patient. Moreover, approximately 8–13% of patients may be completely asymptomatic, usually due to a small (less than 5 mm) tumor or a dedifferentiated tumor without catecholamine-synthesizing enzymes [13, 14]. As a result, PHEOs/PGLs are often missed and are not discovered until autopsy [5, 10, 15]. Patients sometimes present with potentially life-threatening conditions due to excessive catecholamine release from a tumor (Table 12.3). PHEO/PGL-induced hemodynamic or metabolic attacks are variable in duration and frequency. They can occur daily or as infrequently as once a few months, lasting from seconds to several hours.

The classical PHEO/PGL symptoms include headaches, profuse sweating, and palpitations. A high number of patients suffer from sustained or paroxysmal hypertension [6, 10]. If these symptoms are present together, they are highly suggestive for PHEO/PGL [7, 10, 13, 18, 19].

Headaches are the most prevalent symptom (up to 90%) in patients with PHEO/PGL. Seriousness of headaches varies from mild to severe, and they can last up to several days [20]. Sweating and diaphoresis occurs in 60–70% of PHEO/PGL patients [7, 20]. Catecholamine effects, specifically epinephrine, on cardiac β-adrenoceptors can manifest as palpitations [7].

Sustained or paroxysmal hypertension, often resistant to treatment, is present in around 90% of PHEO/PGL patients. Those with sustained high blood pressure present disturbances in the diurnal blood pressure rhythm, reflected by the lack of nocturnal blood pressure dip [21, 22]. Hypertensive PHEO/PGL patients may also

Table 12.2 Differential diagnosis of PHEO/PGL

System	Diagnosis
Endocrine	Adrenal medullary hyperplasia Hyperthyreosis, thyrotoxicosis Carcinoid Hypoglycemia, insulin reaction Medullary thyroid carcinoma Hyperadrenergic essential hypertension Mastocytosis Menopausal syndrome
Cardiovascular	Heart failure Arrhythmias Ischemic heart disease, angina pectoris Myocardial infarction Mitral valve prolapse Abdominal catastrophe/aortic dissection Baroreflex failure Syncope Orthostatic hypotension Labile hypernoradrenergic essential hypertension Renovascular disease
Neurological	Migraine or cluster headaches Stroke Diencephalic autonomic epilepsy Meningioma Paroxysmal tachycardias including postural tachycardia syndrome Guillain-Barré syndrome Encephalitis Intracranial lesions Cerebral vasculitis and hemorrhage
Psychogenic	Anxiety or panic attacks Factitious use of drugs Somatization disorder Hyperventilation
Pharmacologic	Tricyclic antidepressant Cocaine Amphetamine Alcohol withdrawal Drugs stimulating adrenergic receptors Abrupt clonidine withdrawal Dopamine antagonists Ingestion of tyramine-containing foods or proprietary cold preparations while taking monoamine oxidase inhibitors Ephedrine-containing drugs Factitious use of various drugs including catecholamines
Other	Neuroblastoma, ganglioneuroma, ganglioneuroblastoma Acute intermittent porphyria Mastocytosis Unexplained flushing spells Recurrent idiopathic anaphylaxis Toxemia of pregnancy Unexplained shock Lead or mercury poisoning

Refs [7, 10, 179]

Table 12.3 Emergency situations associated with PHEO/PGL

Clinical setting	Symptoms
Pheochromocytoma multisystem crisis (PMC)	Hyper- and/or hypotension Multiple organ failure Body temperature ≥ 40 °C Encephalopathy
Cardiovascular	Collapse Hypertensive crisis Hypertensive crisis upon induction of anesthesia Hypertensive crisis induced by medication or other mechanisms Shock or profound hypotension Acute heart failure Myocardial infarction Arrhythmia Cardiomyopathy Myocarditis Dissecting aortic aneurysm Limb and/or organ ischemia, digital necrosis, or gangrene
Pulmonary	Acute pulmonary edema Adult respiratory distress syndrome Pulmonary hypertension
Abdominal	Abdominal bleeding Paralytic ileus Acute intestinal obstruction Severe enterocolitis and peritonitis Colon perforation Bowel ischemia and generalized peritonitis Mesenteric vascular occlusion Acute pancreatitis Cholecystitis Megacolon Watery diarrhea syndrome with hypokalemia
Neurological	Hemiplegia Limb weakness General muscle weakness Generalized seizures Stroke
Renal	Acute renal failure Acute pyelonephritis Severe hematuria Renal artery stenosis by compression of tumor
Metabolic	Diabetic ketoacidosis Lactic acidosis
Ocular	Acute blindness Retinopathy

Refs [12, 16, 17]

exhibit decreased cardiac output [23] or can present with an acute catecholamine cardiomyopathy/myocardial damage [24–26]. Severe hypertension may result in emergency situations requiring immediate medical attention and treatment [7]. Hypertensive crisis and symptoms associated with paroxysmal blood pressure elevations can occur due to excessive catecholamine release triggered by accidental tumor manipulation during diagnostic procedures (e.g., endoscopy), an increase in intra-abdominal pressure (e.g., palpation, defecation, urination, accident), and administration of anesthesia or certain drugs (Table 12.4) or through ingestion of food and beverages containing tyramine (certain cheeses, beers, wines, bananas, chocolate) or synephrine (citrus fruit juice) [10, 28, 30–34].

Although hypertension is the most common clinical sign, some patients (up to 10%) may have normal blood pressure or may present with hypotension, particularly postural hypotension, or alternating episodes of hyper- and hypotension [13, 35–37]. Orthostatic hypotension is usually accompanied by orthostatic tachycardia and is seen in epinephrine-secreting PHEO/PGL.

Other PHEO/PGL symptoms include flushing or pallor, nausea and vomiting (often exercise induced), anxiety or panic attacks, dyspnea, weight loss despite nor-

Table 12.4 Medications contraindicated in patients with known or suspected PHEO/PGL

Drug class	Examples	Relevant clinical uses
β-Adrenergic receptor blockers[a]	Propranolol, sotalol, timolol, nadolol, labetalol	But may be used to treat conditions that result from catecholamine excess (hypertension, cardiomyopathy, heart failure, panic attacks, migraine, tachycardia, cardiac arrhythmias)
Dopamine D2 receptor antagonists including antipsychotics	Metoclopramide, sulpiride, amisulpride, tiapride, chlorpromazine, prochlorperazine, droperidol	Control of nausea, vomiting, psychosis, hot flashes, tranquilizing effects
Tricyclic antidepressants and norepinephrine reuptake inhibitors	Amitriptyline, imipramine, nortriptyline, clomipramine	Treatment of insomnia, neuropathic pain, nocturnal enuresis in children, headaches, depression (rarely)
Other antidepressants (serotonin reuptake inhibitors)	Paroxetine, fluoxetine, duloxetine	Depression, anxiety, panic attacks, antiobesity agents
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine	Nonselective agents rarely used as antidepressants (owing to “cheese effect”)

(continued)

Table 12.4 (continued)

Drug class	Examples	Relevant clinical uses
Sympathomimetics[a]	Ephedrine, pseudoephedrine, fenfluramine, amfepramone, phendimetrazine, methylphenidate, phentermine, dexamfetamine	Control of low blood pressure during surgical anesthesia, as decongestants, antiobesity agents
Chemotherapeutic agents[a]		Antineoplastic actions and treatment of malignant pheochromocytoma
Oxazolidinone antibiotics	Linezolid	Treatment of infections caused by multiresistant gram-positive bacteria
Opioid analgesics[a] and naloxone	Morphine, pethidine, tramadol, oxycodone, heroin	Induction of surgical anesthesia
Neuromuscular blocking agents[a]	Succinylcholine, tubocurarine, atracurium	Induction of surgical anesthesia
Peptide and steroid hormones[a]	ACTH, glucagon, dexamethasone, prednisone, hydrocortisone, betamethasone	Diagnostic testing
Illegal recreational drugs	Ketamine, cocaine	
Chewing tobacco		

Partially adapted from [6, 27–29]

[a]These drugs have therapeutic or diagnostic use in PHEO/PGL, but usually only after pretreatment with appropriate antihypertensives (e.g., α-adrenoceptor blockers)

mal appetite, warmth with or without heat intolerance, or general weakness [6, 7, 35]. Less commonly, PHEO/PGL presents as fever of unknown origin, constipation due to catecholamine-induced decrease in intestinal motility, or cholesterol gallstones [38–40]. Due to the metabolic effects of epinephrine, hyperglycemia with low levels of plasma insulin associated with hypertensive episodes can occur. PHEOs/PGLs can also cause insulin resistance and diabetes mellitus manifestation [7, 41–47]. Rarely, PHEOs/PGLs can produce vasoactive intestinal peptide resulting in watery diarrhea, hypokalemia, and achlorhydria [48].

Patients may also complain of symptoms resulting from compression of tissues surrounding the tumor. For example, tumors located in the abdomen or chest can cause abdominal or chest pain. Patients with PGLs of the neck can present with dysphagia and dysphonia, and those with tumors growing in the head and neck area can display tinnitus, hearing loss, or cranial nerve palsy [49].

Since PHEO/PGL can have potentially life-threatening consequences, recognizing the signs and symptoms of these tumors leading to appropriate diagnostic sequence is critical. Evaluation for PHEO/PGL should be warranted in patients: (a) with a family history of PHEO/PGL or certain hereditary cancer syndromes (Table 12.5); (b) presenting with hypertension, tachycardia, sweating, and pallor; (c) presenting with resistant hypertension; (d) presenting with any paroxysmal symptoms; (e) presenting with hypertension and other symptoms in response to examination, anesthesia, surgery, certain medications, or foods and drinks; and (f) with adrenal incidentalomas [7, 11, 17, 51].

Table 12.5 Susceptibility genes and hereditary cancer syndromes associated with PHEO/PGL development and genotype-phenotype correlations

Molecular cluster	Gene	Locus	Mutation type	Inheritance	Syndrome	PHEO/PGL penetrance	Biochemical phenotype	Typical tumor localization	Malignancy rate	Associated clinical characteristics/other tumors
Krebs cycle (cluster 1a)	*SDHA*	5p15	Germline	AD	PGL5	Unknown	Unknown	HNPGL/ TAPGL	0–14%	• Homozygots: Leigh's syndrome • Clear cell renal carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas
	SDHB	1p36.13	Germline and somatic	AD	PGL4	30–100%	MN, NMN, MTY, NS	TAPGL; rarely HNPGL/ adrenal	31–71%	• Clear cell renal carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas • Possibly breast carcinoma • Possibly papillary thyroid carcinoma
	SDHC	1q23.3	Germline	AD	PGL3	Unknown	MN, NMN, MTY, NS	HNPGL; rarely TAPGL/ adrenal	Low	• Clear cell renal carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas
	SDHD	11q23	Germline and somatic	AD PI	PGL1	73–90%	MN, NMN, MTY, NS	HNPGL; rarely TAPGL/ adrenal	Low (<5%)	• Clear cell renal carcinoma • Gastrointestinal stromal tumors • Pituitary adenomas
	SDHAF2	11q12	Germline	AD PI	PGL2	100%	Unknown	HNPGL	Unknown	
	FH	1q42.1	Germline	–		Unknown	NMN	Adrenal/ TAPGL	Unknown (High?)	• Leiomyomatosis of skin and uterus • Clear cell renal carcinoma
	MDH2	7q11.23	Germline	–		Unknown	Unknown (NMN?)	Unknown (TAPGL?)	Unknown	

(continued)

Table 12.5 (continued)

Molecular cluster	Gene	Locus	Mutation type	Inheritance	Syndrome	PHEO/PGL penetrance	Biochemical phenotype	Typical tumor localization	Malignancy rate	Associated clinical characteristics/other tumors
Pseudohypoxic (cluster 1b)	*VHL*	3p25.3	Germline and somatic	AD	Von Hippel-Lindau	10–20%	NMN	Adrenal; rarely TAPGL/HNPGL	Low (<5%)	• Hemangioblastomas • Clear cell renal carcinoma • Tumors of pancreatic islets • Retinal angioma • Retinal, pancreatic, and testicular cysts
	HIF2A	2p21	Germline[a] and somatic	–	Pacak-Zhuang syndrome	Unknown	NMN	TAPGL/adrenal	Unknown	• Somatostatinoma, often multiple • Polycythemia • Eye changes • Organ cysts
	PHD1/EGLN2	19q13.2	Germline	–		Unknown	NMN	Unknown	Unknown	• Polycythemia
	PHD2/EGLN1	1q42.2	Germline	–		Unknown	NMN	Unknown (TAPGL?)	Unknown	• Polycythemia
Kinase signaling (cluster 2)	*NF1*	17q11.2	Germline and somatic	AD	Neurofibromatosis type 1	<6%	MN, NMN	Adrenal; rarely TAPGL	11%	• Café au lait spots • Neurofibromas • Freckles • Benign hamartomas of iris (Lisch nodules) • Gliomas and optical gliomas • Duodenal somatostatinomas • Sphenoid dysplasia/pseudoarthritis

RET	10q11.21	Germline and somatic	AD	MEN2	50%	MN, NMN	Adrenal	Low (<1–5%)	• Medullary thyroid carcinoma • Hirschsprung's disease • Hyperparathyreosis/ hypercalcemia (MEN2A) • Marfanoid habitus, ganglioneuromas (MEN2B)
TMEM127	2q11.2	Germline	–		Unknown	MN and NMN	Adrenal/ TAPGL/ HNPGL	Low (4%)	• Possibly breast carcinoma • Possibly papillary thyroid carcinoma
MAX	14q23.3	Germline and somatic	–		Unknown	NMN and MN	Adrenal	10–25%	• Neuroblastoma
KIF1Bβ	1p36.22	Germline	–		Unknown	Unknown	Unknown (adrenal?)	Unknown	• Lung, colorectal adenocarcinoma • Neuroblastoma
H-RAS	11p15.5	Somatic	–		N/A	MN, NMN	Adrenal/ TAPGL	Unknown	
K-RAS		Somatic	–		N/A	Unknown	Adrenal	Unknown	
ATRX	Xq21.1	Somatic	–		N/A	Unknown	Unknown (adrenal? TAPGL?)	Unknown	

AD autosomal dominant, *ATRX* alpha thalassemia/mental retardation syndrome X-linked, *EGLN1/2* Egl-9 family hypoxia-inducible factor 1/2, *FH* fumarate hydratase, *HIF2A* hypoxia-inducible factor 2α, *HRAS* Harvey rat sarcoma viral oncogene homolog, *HNPGL* head and neck paraganglioma, *IDH* isocitrate dehydrogenase, *KIF1Bβ* kinesin family member 1B, *MAX* myc-associated factor X, *MDH2* malate dehydrogenase 2, *MEN2A/2B* multiple endocrine neoplasia, type 2A/2B, *MN* metanephrine, *MTY* methoxytyramine, *NF1* neurofibromin 1, *NMN* normetanephrine, *NS* nonsecreting, *PGL* paraganglioma, *PHD1/2* prolyl hydroxylase domain-containing protein 1/2, *PHEO* pheochromocytoma, *PI* paternal inheritance, *RET* rearranged during transfection proto-oncogene, *SDHA*, *SDHB*, *SDHC*, *SDHD* succinate dehydrogenase subunits A, B, C, and D, *SDHAF2* SDH complex assembly factor 2, *TMEM127* transmembrane protein 127, *TAPGL* thoracic and abdominal paraganglioma, *VHL* von Hippel-Lindau [6, 50]

[a]Present as PHEO/PGL with polycythemia only, most probably differ from presentation and characteristics of tumors associated with somatic *HIF2A* mutations

Biochemical Diagnosis of Pheochromocytoma

Initial Biochemical Testing

Most PHEOs and PGLs are characterized by excessive production of catecholamines, and thus, biochemical evidence of catecholamine production is an elementary step in diagnosis. Historically, biochemical diagnosis of PHEO/PGL relied on the measurement of urinary and plasma catecholamines (epinephrine and norepinephrine) together with measurement of urinary levels of catecholamine metabolites and vanillylmandelic acid. These tests can often lead to false negatives due to fluctuating levels of catecholamine release in many PHEOs/PGLs [10, 28]. Since PHEOs/PGLs often secrete catecholamines episodically, plasma or urinary levels of catecholamines may be normal. Approximately 30% of PHEOs/PGLs do not secrete catecholamines, even if they still synthesize them or they do not secrete catecholamines in amounts sufficient enough to produce the classical clinical presentation of a tumor with positive test results [52, 53]. Moreover, catecholamines are normally produced by the adrenal medulla and sympathetic nerves. Thus, high catecholamine levels are present in multiple different diseases and conditions and are not specific for these tumors [53].

On the other hand, metanephrines, the O-methylated metabolites of catecholamines, are produced continuously within PHEO/PGL cells, and their production is independent of catecholamine release [54, 55]. Therefore, diagnostic evaluation of plasma-free or urine-fractionated (i.e., normetanephrine and metanephrine measured separately) metanephrines is preferred and is currently the most sensitive diagnostic test (97% sensitivity and 93% specificity for measurement for plasma-free metanephrines) [8, 56–63]. Plasma metanephrines are usually measured in the free form. Metanephrines in urine are measured after deconjugation, although measurement of urine-free metanephrines is also possible [64, 65].

When interpreting the results, differentiating between a mild and high increase in catecholamine or metanephrine levels is very important. In patients with biochemically active tumors, an increase is usually two to four times higher than the upper reference limit. Mildly elevated levels of catecholamines are mostly due to interfering medications [10] (Table 12.6). If it is difficult to distinguish an increased catecholamine release due to sympathetic activation or from the presence of PHEO/PGL, a clonidine suppression test can be performed [66, 67]. Under physiologic conditions, clonidine suppresses release of neuronal norepinephrine (and so normetanephrine). A decrease in elevated plasma normetanephrine levels by ≥40% or within the reference limits after clonidine is administered indicates that sympathetic activation is the cause of elevation. Failure to depress plasma normetanephrine supports the presence of PHEO/PGL [67]. The clonidine suppression test has a high diagnostic sensitivity when combined with measurement of plasma normetanephrine responses to suppression. False positive elevations in plasma normetanephrine levels can be accurately identified with the combination of these tests. However, the reliability of the test can be compromised by tricyclic antidepressants

Table 12.6 Compounds that may cause false-positive elevations of plasma and urinary catecholamines or metanephrines

Compound group	Examples	Catecholamines		Metanephrines	
		NE	E	NMN	MN
Tricyclic antidepressants	Amitriptyline, imipramine, nortriptyline	+++	–	+++	–
α-Blockers (nonselective)	Phenoxybenzamine	+++	–	+++	–
α-Blockers (α_1-selective)	Doxazosin, terazosin, prazosin	+	–	–	–
β-Blockers	Atenolol, metoprolol, propranolol, labetalol	+	+	+	+
Calcium channel antagonists	Nifedipine, amlodipine, diltiazem, verapamil	+	+	–	–
Vasodilators	Hydralazine, isosorbide, minoxidil	+	–	?	?
Monoamine oxidase inhibitors	Phenelzin, tranylcypromine, selegiline	–	–	+++	+++
Sympathomimetics	Ephedrine, pseudoephedrine, amphetamines, albuterol	++	++	++	++
Stimulants	Caffeine, nicotine, theophylline	++	++	?	?
Miscellaneous	Levodopa, carbidopa Cocaine	++ ++	– ++	? ?	? ?

Partially adapted from [8]
E epinephrine, *MN* metanephrine, *NE* norepinephrine, *NMN* normetanephrine, +++ substantial increase, ++ moderate increase, + mild increase, – little or no increase, ? unknown

and diuretics [42], as well as in patients with normal or only mildly elevated plasma catecholamine levels, despite the presence of PHEO/PGL [8].

In addition to measurement of metanephrines, recent evidence suggests that plasma 3-methoxytyramine is a biomarker for dopamine-producing tumors. Although it is currently only available in certain research centers, measurements of this biomarker are valuable for detecting very rare, exclusively dopamine-producing tumors (due to the lack of dopamine β-hydroxylase), which can be easily overlooked by solely measuring metanephrines [68, 69]. Moreover, methoxytyramine can also serve as an indicator of malignancy [4]. Exclusively dopamine-secreting tumors can also be detected by measuring serum levels of dopamine. Measurement of urinary dopamine levels is not useful, since it reflects dopamine production in the renal tubules, not in a potential tumor [27].

A nonspecific biomarker of neuroendocrine tumors, chromogranin A, is often measured in PHEO/PGL patients. Chromogranin A is commonly secreted by chromaffin cells, and its levels are elevated in 91% of patients with PHEO/PGL [70]. Despite its nonspecificity, chromogranin A, in combination with catecholamine measurement, can facilitate the diagnosis of PHEO/PGL, especially in tumors related to mutations in succinate dehydrogenase (SDH) subunit B gene [71, 72]. Chromogranin A is also a helpful diagnostic tool in patients with biochemically silent tumors and in disease monitoring [73, 74].

In very rare cases, PHEOs/PGLs can co-secrete other hormones, for example, ACTH or cortisol. These patients often present with the clinical picture of Cushing disease in addition to PHEO/PGL [75–77].

Determining the biochemical phenotype of PHEO/PGL can also be helpful in navigating further investigation and treatment, specifically localization of the tumor by imaging studies, genetic screening, determining the presence of metastatic disease, and an appropriate adrenergic blockade. Based on the type of catecholamines secreted, PHEOs/PGLs can be divided into three basic biochemical phenotypes: (a) adrenergic (epinephrine/metanephrine), (b) noradrenergic (norepinephrine/normetanephrine), and (c) dopaminergic (dopamine/methoxytyramine). Mixed phenotypes are common, and in such cases, PHEO/PGL-producing metanephrine and normetanephrine are considered adrenergic, and those secreting normetanephrine and methoxytyramine are considered dopaminergic. Since epinephrine/metanephrine are produced almost exclusively (99%) in the adrenal gland, adrenergic biochemical phenotype is typical for PHEO (Table 12.5).

Follow-Up Biochemical Testing

Although PHEOs/PGLs are rare tumors, a large number of patients are tested for these tumors in the process of differential diagnosis for secondary hypertension as well as other diseases. Because of this, false-positive results are expected, and they may outnumber true-positive results, even when tests with high specificities are used. This requires follow-up biochemical testing in patients with initially positive results, to confirm or rule out PHEO/PGL. However, when judging the likelihood of a PHEO/PGL from a single test, the degree of initial clinical suspicion or pretest probability of the tumor should be taken into account, which impacts the posttest probability of a tumor [7]. Moreover, patients with known hereditary syndromes associated with PHEO/PGL or with a history of tumors should periodically undergo screening. Biochemical testing is also used to confirm the success of surgical treatment and to evaluate activity of the disease in patients with metastases.

Sample Collection and Test Interferences

To ensure the reliability of biochemical test results, it is crucial to guarantee certain conditions during blood sample collection. Before collection of blood for measurements of plasma-free metanephrines, patients should be lying supine in a quiet room for at least 20–30 min with a previously inserted intravenous line (to minimize sympathoadrenal activation associated with venipuncture or upright posture) [53, 78]. Alternatively, with a higher risk of false-positive results, the sample may be collected from a seated patient, provided that upper reference limits obtained after supine rest are used [79]. If seated test returns back positive, it should be repeated after rest in supine position to rule out false positivity of initial test [8].

Although 24-h urine collection seems to solve the problem with the rigid conditions needed for blood sampling, it is not that simple. Twenty-four-hour urine results are not always accurate because of unreliable collection from the patient. Samples are also often influenced by diet and the activation of sympathoneuronal and adrenal medullary systems (e.g., during physical activity or changes of posture). To ensure more controlled conditions for urine collection, some investigators advocate spot or overnight urine collections with normalization of output catecholamines or metanephrines against urinary creatinine excretion [8, 80].

Blood samples should be stored on ice immediately after collection and separated plasma at −80 °C upon analysis. Urine samples should be refrigerated during the collection period while using HCl as a preservative. Urine sample aliquots should be stored frozen at −80 °C to minimize auto-oxidation and deconjugation [53].

When evaluating a patient for possible PHEO/PGL, it is necessary to ask the patient about their current medications. Certain compounds can increase catecholamine levels or interfere with the diagnostic analysis and, thus, result in catecholamine/metanephrine false positives [78]. The major source of interference is tricyclic antidepressants, which can lead to significant elevation of plasma or urinary metanephrines due to inhibition of catecholamine reuptake. Acetaminophen, a drug commonly used for pain and fever, as well as mesalamine and sulfasalazine, can interfere with high-performance liquid chromatographic (HPLC) assays used for measurement of catecholamines [67, 81]. An anxiolytic agent, buspirone, can cause falsely elevated levels of urinary metanephrine in some HPLC assays [67]. Other compounds that may distort catecholamine/metanephrine measurements are listed in Table 12.6.

Localization of Pheochromocytoma

PHEO/PGL localization should only be initiated if clinical evidence for the presence of a tumor is reasonably convincing and biochemical results are strongly positive [28, 59]. If biochemical evidence of a tumor is not compelling, imaging is only justified in patients with a higher probability of tumor development, such as those with hereditary predisposition, previous history of the tumor, or evidence of biochemically silent tumor in carriers with one of the PHEO/PGL susceptibility genes [8, 59]. Based on the tumor biochemical profile, imaging can initially be focused on certain areas of the body. In patients with elevated metanephrine/epinephrine levels, imaging should primarily center on the adrenal gland, as adrenergic phenotype is associated mostly with adrenal tumors. If the scan of adrenal glands is normal, imaging of additional areas of the body should be performed, specifically the abdomen, pelvis, chest, and neck (“eyes to thighs”). A detailed history and careful physical examination may also provide critical information about the possible location of a PHEO/PGL. For instance, postmicturition hypertension suggests urinary bladder PGL [8].

According to expert recommendations, optimal results for PHEO/PGL localization and confirmation are achieved by performing anatomical imaging studies (computed tomography (CT) and magnetic resonance imaging (MRI)) in combination

with functional (nuclear medicine) imaging studies [59]. Functional imaging is very useful in detecting primary or metastatic tumors, which could be missed with anatomical modalities [6]. Moreover, imaging plays an important role in the decision-making approach. For example, identification of multiple lesions or metastases before an initial surgery may completely change the treatment plan [8]. An algorithm for localization of PHEO/PGL is depicted in Fig. 12.1. Imaging is also an important part of screening patients with known genetic predisposition to PHEO/PGL development and for follow-up for patients with a history of PHEO/PGL. For

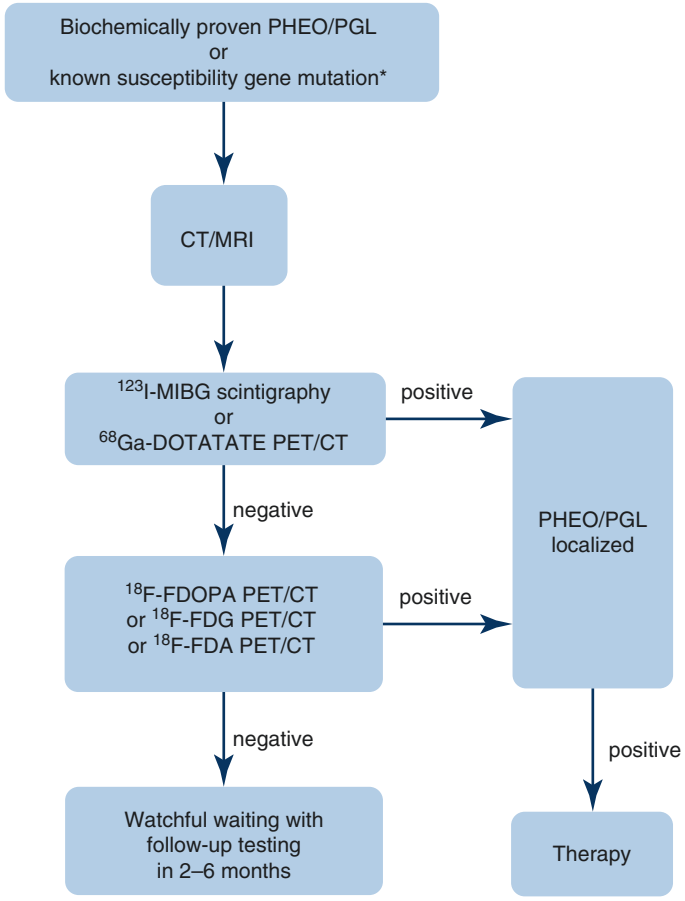

Fig. 12.1 Algorithm for localization of PHEO/PGL. In patients with a biochemically proven PHEO/PGL, as well as in patients with a susceptibility gene mutation known to be associated with a nonsecretory phenotype, anatomic imaging of adrenals/abdomen is suggested. If the result is negative, chest and neck CT or MRI scans should be performed. Afterward, the presence of PHEO/PGL should be confirmed or ruled out with functional imaging [8]. *^{18}F-FDA* ^{18}F-fluorodopamine, *^{18}F-FDG* ^{18}F-fluorodeoxyglucose, *^{18}F-FDOPA* ^{18}F-dihydroxyphenylalanine, *^{68}Ga-DOTATATE* ^{68}Ga-DOTA(0)-Tyr(3)-octreotate, *^{123}I-MIBG* ^{123}I-metaiodobenzylguanidine, *CT* computed tomography, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *PGL* paraganglioma, *PHEO* pheochromocytoma

genetic mutation carriers, CT or MRI is recommended every few years along with biochemical evaluation. This is particularly important for carriers of the mutations in genes encoding succinate dehydrogenase subunits (*SDHx*: *SDHA*, *SDHB*, *SDHC*, *SDHD*) and patients with head and neck PGLs, as these patients often present with biochemically silent tumors [28, 82].

Anatomical Imaging

Anatomical imaging of PHEO/PGL should initially focus on the abdomen and pelvis, followed by the chest and neck if abdominal and pelvic scans are negative [59]. Computed tomography and MRI are widely used in the diagnostic workup for PHEO/PGL, and these modalities have been reported to have similar diagnostic sensitivities [10], although MRI may be superior to CT in detecting extra-adrenal tumors in certain locations (e.g., cardiac) [8]. Ultrasound is not recommended for initial PHEO/PGL localization. Exceptions include ruling out tumors in children and pregnant women, when MRI is not available.

Excellent spatial resolution, wider availability, and a relative low cost suggest a CT scan of the abdomen, with or without contrast, as an initial PHEO/PGL localization method [28]. Computed tomography can be used to localize tumors 1 cm or larger. The sensitivity of CT is approximately 95%, with specificity roughly 70% [83]. Use of intravenous contrast media is preferred to enhance the specificity of the method. However, the CT scan may fail to localize recurrent PHEOs/PGLs because of postoperative anatomical changes and the presence of surgical clips.

An MRI with or without gadolinium enhancement is a very dependable imaging method with sensitivity >95% and specificity similar to CT (70–80%) [10, 84, 85]. MRI has a high sensitivity in detecting adrenal lesions (93–100%) and is a good imaging modality for the detection of intracardiac, juxtacardiac, and juxtavascular PGLs. Moreover, MRI offers feasibility of multiplanar imaging and superior assessment of the relationships between tumor and surrounding vessels. This is important in the evaluation of patients with tumors in the adrenal and cardiac areas and for ruling out vessel invasion. The sensitivity of MRI for detection of extra-adrenal, metastatic, or recurrent PHEOs/PGLs is around 90%. Thus, MRI is preferred in patients with head and neck PGLs and metastatic disease and in patients with CT contrast allergies or in whom radiation exposure is contraindicated (pregnant women, children, patients with known germline mutations, patients with recent excessive radiation exposure) [10, 28].

Functional Imaging

Functional imaging plays an important role in PHEO/PGL workup. Specificity of anatomical imaging studies for PHEO/PGL is not sufficient. Thus, functional studies are needed to confirm the presence of a PHEO/PGL. Functional imaging may also help detect primary and/or metastatic tumors that could be missed on anatomical studies. It is also used to characterize the metabolic activity of the tumors in vivo and for

restaging aggressive tumors following treatment completion [86]. Functional imaging studies are enabled by the presence of the cell membrane and/or vesicular catecholamine transport systems in PHEO/PGL cells. Functional imaging modalities used to confirm PHEO/PGL and/or metastatic disease include ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG)scintigraphy,6-^{18}F-fluorodopamine(^{18}F-FDA),^{18}F-dihydroxyphenylalanine (^{18}F-DOPA), ^{11}C-hydroxyephedrine, and ^{11}C-epinephrine (not used anymore) positron emission tomography (PET) [87–93]. Currently, these methods are not widely available, and if needed, patients are referred to specialized centers.

In metastatic PHEO/PGL, tumor dedifferentiation may lead to loss of specific neurotransmitter transporters, resulting in difficulties with its localization. In such cases, ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging or somatostatin receptor scintigraphy may be required. Metastatic PHEOs/PGLs often express somatostatin receptors, which enables somatostatin scintigraphy with the somatostatin analogue octreotide (octreoscan) or DOTA peptides analogues (^{68}Ga-DOTA(0)-Tyr(3)-octreotate (DOTATATE) PET/CT) [94–97].

Metaiodobenzylguanidine Scintigraphy

Historically, functional imaging has been performed using MIBG labeled with radioactive iodine (^{123}I and ^{131}I). MIBG is an aralkylguanidine similar to norepinephrine. ^{131}I-MIBG scintigraphy is not used for imaging because of its longer half-life and lower sensitivity (50%) compared to ^{123}I-MIBG (92–98% in nonmetastatic tumors, 57–79% for metastases) [90, 98–103]. Although the sensitivity of ^{123}I-MIBG for detection of metastases is low, it is very useful in identification of patients who can possibly benefit from palliative treatment with therapeutic doses of ^{131}I-MIBG. Besides PHEOs/PGLs, ^{123}I-MIBG uptake also occurs in other neuroendocrine tumors, such as glomus tumors, carcinoids, or in the sporadic and familial medullary carcinomas of the thyroid. $^{123/131}$I-MIBG is physiologically accumulated in the myocardium, spleen, liver, urinary bladder, lungs, salivary glands, large intestine, and cerebellum. Furthermore, in 75% of patients, uptake is shown in normal adrenal glands.

Before MIBG scintigraphy, it is important to withhold the drugs interfering with accumulation of MIBG—it is suggested to do so for 2 weeks prior to exam. Interfering drugs include compounds that deplete catecholamine stores, compounds that inhibit cell catecholamine transporters, and other drugs such as calcium channel blockers or certain α- and β-blockers (Table 12.7) [104–106]. Appropriate blockade with potassium iodide, potassium iodate, 1% Lugol's solution, or potassium perchlorate is required to prevent an uptake and accumulation of free iodide ($^{123/131}$I) in the thyroid gland [104].

Imaging scans are performed at 24 h and again at either 48 or 72 h after injection of the radioisotope, to decipher whether images from earlier scan are tumors or are physiological and fading out.

Table 12.7 Compounds interfering with MIBG uptake by tumors

Interfering agent group	Example	Mechanism of interference	Length of discontinuation before MIBG imaging/ treatment
Combined α-/β-blocker	Labetalol	MIBG uptake inhibition	72 h
Adrenergic neurons blockers	Reserpine, bretylium	MIBG storage depletion	48 h
Calcium channel blockers	Amlodipine, diltiazem, nifedipine	MIBG uptake inhibition	48–72 h
Inotropic sympathomimetics	Dobutamine, dopamine	MIBG storage depletion	24 h
Vasoconstrictor sympathomimetics	Ephedrine, phenylephrine, norepinephrine	MIBG storage depletion	24–48 h
β2 adrenoceptor stimulants (sympathomimetics)	Salbutamol, terbutaline, fenoterol	MIBG storage depletion	24 h
Other adrenoceptor stimulants	Orciprenaline	MIBG storage depletion	24 h
Sympathomimetics for glaucoma	Brimonidine, dipivefrine	MIBG storage depletion	48 h
Tricyclic antidepressants	Amitriptyline, clomipramine, nortriptyline	MIBG uptake inhibition	24–48 h
Tricyclic-related antidepressants/ atypical antidepressants	Maprotiline, trazodone, venlafaxine, mirtazapine	MIBG uptake inhibition	48 h–8 days
Antipsychotics (neuroleptics)	Chlorpromazine, haloperidol, perphenazine, risperidone	MIBG uptake inhibition	24 h–7 days, 1 month for depot forms
CNS stimulants	Amphetamines, cocaine, caffeine, phenylpropanolamine	MIBG uptake inhibition/MIBG storage depletion/ unknown	24 h–5 days
Sedating antihistamines	Promethazine	MIBG uptake inhibition	24 h
Systemic and local nasal decongestants, compound cough and cold preparations	Pseudoephedrine, phenylephrine, phenylpropanolamine	MIBG storage depletion	48 h
Opioid analgesics	Tramadol	MIBG uptake inhibition	24 h

Refs [104, 105]

Positron Emission Tomography

PET has become a more widely available and valuable imaging method, offering high sensitivity, shorter acquisition times, low radiation exposure, and superior spatial resolution [86, 107]. Moreover, PET provides a quantifiable estimate of tumor metabolism using standard uptake values (SUV) [86].

Most of the tumors, including PHEO/PGL, exhibit increased glucose metabolism, which enables the use of glucose labeled with ^{18}F (fluoride) for imaging [91, 92]. ^{18}F-FDG PET is highly sensitive for the detection of metastatic PHEO/PGL (approx. 90%), especially in patients harboring SDH subunit B (*SDHB*) gene mutations. Sensitivity of ^{18}F-FDG PET for detection of primary, nonmetastatic PHEOs/PGLs is 88%, with a specificity similar to that of ^{123}I-MIBG. Thus, ^{18}F-FDG PET/CT is recommended for localization of metastatic disease [28, 108].

The majority of the radiopharmaceuticals used for PET detection of PHEO/PGL enter the tumor cell using the cell membrane norepinephrine transporter. A positron emitting analogue of dopamine, 6-^{18}F-FDA, is a very useful sympathoneuronal PET imaging agent for catecholamine-synthesizing cells [109]. ^{18}F-FDA PET has a high sensitivity for both primary PHEOs/PGLs and metastases (77–100% and 77–90%, respectively), with specificity more than 90% [100, 108]. Unfortunately, ^{18}F-FDA PET/CT is not yet widely available. Other PET imaging tracers, ^{11}C-hydroxyephedrine and ^{11}C-epinephrine, have been shown to only have limited application in diagnostic imaging because of the short half-life of ^{11}C (20 min) [110, 111].

^{18}F-DOPA is an amino acid analogue and catecholamine precursor that is taken up by the amino acid transporter [112]. Pretreatment with carbidopa enhances tumor uptake of tracer and improves sensitivity due to inhibition of DOPA decarboxylase [113]. ^{18}F-DOPA is extremely sensitive (81–100%) for the localization of nonmetastatic PHEO/PGL and head and neck PHEO/PGL [87, 108, 114, 115]. However, for detection of metastatic and *SDHB* mutation-related PHEOs/PGLs, sensitivity is not satisfactory (45% and 20%, respectively) [8].

Somatostatin Receptor-Based Imaging

Somatostatin receptors are expressed in up to 73% of PHEO/PGL cells in vitro [116], and scintigraphy using octreotide (^{111}In-pentreotide) has been used for PHEO/PGL localization, specifically for localization of head and neck PGLs. However, the sensitivity of this imaging modality is low, and thus, it is inferior to ^{123}I-MIBG scintigraphy [117]. Still, octreoscan can be useful in detection of tumors that express somatostatin receptors and are negative on other scans [118].

For somatostatin receptor-based PET/CT imaging, radiolabeled DOTA peptide analogues (DOTATATE, DOTATOC, and DOTANOC) were shown to be superior to all other imaging methods. For instance, ^{68}Ga-labeled DOTA peptides have been found to be highly sensitive for localization of neuroendocrine tumors, including PHEO/PGL [96, 97, 119–126]. In recent studies from Janssen et al. [94, 95], ^{68}Ga-DOTATATE PET/CT was shown to be clearly superior to all other functional imaging modalities, including ^{18}F-FDG PET/CT, ^{18}F-FDOPA PET/CT, and ^{18}F-FDA PET, for localization of both sporadic and *SDHB*-related metastatic PHEO/PGL.

The costs of imaging based on radiolabeled DOTA peptides are comparable to ^{18}F-FDG PET or ^{123}I-MIBG scintigraphy. These new modalities are expected to be more broadly available in few years.

Genetic Testing

From a clinical point of view, it is necessary to consider genetic testing in addition to diagnostics and appropriate therapy, especially in patients with a suspected hereditary form of the disease and in their first-step relatives. If the PHEO/PGL susceptibility germline mutation is present, patients need to be screened regularly, even if the disease is not obvious. Particular gene mutations present with a specific clinical and biochemical phenotype. Early identification of a mutation allows a physician to predict the course of disease, risk of malignancy, and heritability and helps to choose an appropriate treatment strategy. In order to diagnose PHEO/PGL and identify a specific mutation, it is necessary to take a comprehensive personal and family history, perform meticulous clinical and biochemical examinations, and use adequate imaging methods. In PHEO/PGL, it is important to particularly assess the location of a tumor, biochemical phenotype, age of a patient, and the presence of any tumors besides PHEO/PGL [6].

Hereditary disease should be suspected in patients from families with two or more cases of PHEO/PGL or with syndromes associated with PHEO/PGL. In syndromic forms of PHEO/PGL, underlying mutations can be predicted based on a combination of characteristic tumor types in the patient or their family members (e.g., renal cell carcinoma and hemangioblastoma or retinal angioma in von Hippel-Lindau (VHL) disease, medullary thyroid cancer in multiple endocrine neoplasia type 2) or based on characteristic clinical phenotype (e.g., café au lait spots and eye symptoms—Lisch nodules, optical gliomas—in neurofibromatosis type 1, polycythemia in mutations in hypoxia-inducible factor 2α (*HIF2A*) gene, Hirschsprung's disease in multiple endocrine neoplasia type 2) [127, 128]. Hereditary PHEO/PGL syndromes, associated tumors, and other characteristics associated with various mutations are in Table 12.5.

From a biochemical point of view, adrenergic mixed phenotype is observed in PHEOs/PGLs associated with *NF1* (neurofibromin 1), *RET* (rearranged during transfection), *KIF1Bβ*, and *MAX* (myc-associated factor X) mutations. *TMEM127* (transmembrane protein 127)-mutated tumors present with high metanephrine concentrations, which means they are solely adrenergic [50, 129]. PHEOs/PGLs associated with mutations in *VHL*, *SDHx*, *SDHAF2* (SDH assembly factor 2), *HIF2A*, *FH* (fumarate hydratase), *IDH* (isocitrate dehydrogenase), and *PHD1/2* (HIF prolyl hydroxylase domain-containing protein 1/2) genes are mostly extra-adrenal, except for *VHL*-mutated tumors [50, 130–132], and usually present with dopaminergic and/or noradrenergic biochemical phenotype [54, 133, 134]. *VHL*- and *HIF2A*-mutated PHEOs/PGLs typically exhibit a noradrenergic phenotype, and *SDHx* tumors are associated with a dopaminergic component. Rarely, they are biochemically silent [50, 129, 133, 134] (Fig. 12.2).

Presence of metastases in PHEO/PGL patient leads to suspicion of *SDHB* or *FH* mutations. Familial forms of PHEO/PGL usually show autosomal dominant inheritance, which means that children of mutation carriers have a 50% chance of inheriting the mutation from a parent. However, we cannot forget about the low penetrance

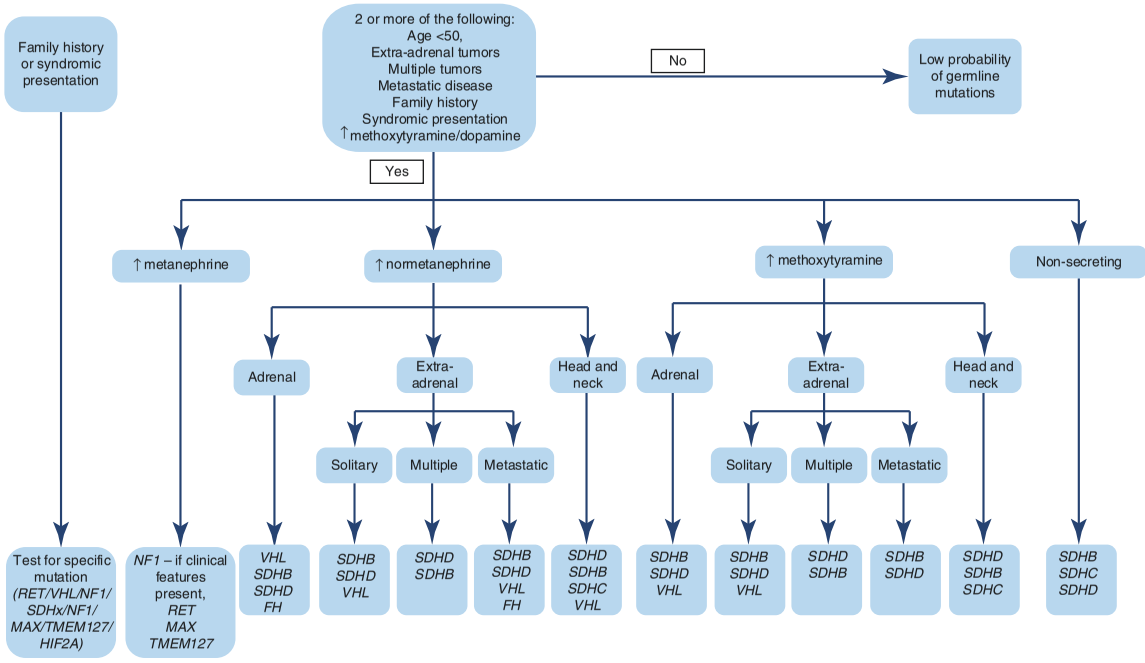

Fig. 12.2 Algorithm for genetic testing based on biochemical phenotype and clinical presentation of PHEO/PGL. In patients with a known family history of PHEO/PGL susceptibility mutation, this mutation should be tested first. Patients presenting with features of one of the syndromes associated with PHEO/PGL (NF1, VHL, MEN2, Pacak-Zhuang, etc.) should be tested for genetic mutations linked to those syndromes. In NF1, diagnosis is usually made on clinical presentation alone, and no genetic testing is needed. In patients without a known family history of PHEO/PGL, the direction of genetic testing is based upon the biochemical profile and localization of the tumor. For some of the known genetic mutations, biochemical profile and/or tumor location has not yet been elucidated (Table 12.5) [6, 135–137]. *FH* fumarate hydratase, *HIF2A* hypoxia-inducible factor 2α, *MAX* myc-associated factor X, *MEN2* multiple endocrine neoplasia, type 2, *NF1* neurofibromin 1, NF1 neurofibromatosis type 1, *PGL* paraganglioma, *PHEO* pheochromocytoma, *RET* rearranged during transfection proto-oncogene, *SDHA*, *SDHB*, *SDHC*, *SDHD* succinate dehydrogenase subunits A, B, C, and D, *SDHx* succinate dehydrogenase complex gene mutations, *TMEM127* transmembrane protein 127, *VHL* von Hippel-Lindau

of PHEO/PGL in some mutations (e.g., *SDHx*)—in these cases, a negative family history does not rule out the presence of a familial form of PHEO/PGL. In *SDHD*, *SDHAF2*, and *MAX* mutations, the risk of disease depends on which parent is the mutation carrier. The disease will only develop if the mutated gene is inherited from the father [138]. Germline mutations are present in 8–24% of apparently sporadic PHEOs/PGLs. These mutations often appear as *de novo* mutations or are associated with low penetrance [127, 128, 139]. In these patients, an underlying gene mutation should be considered if the tumor is extra-adrenal and malignant or if the diagnosis of PHEO/PGL is made at an early age [136].

Management of Patient with PHEO/PGL

Appropriate management of patients with PHEO/PGL requires a close collaboration of several specialists, including an endocrinologist, internist, radiologist, anesthesiologist, surgeon, and, if needed, oncologist [10, 59]. Currently, the only available curative treatment for PHEO/PGL is surgery. Thus, the optimal therapy for PHEO/PGL is a prompt, ideally complete, surgical removal of the tumor to prevent potentially life-threatening complications. Surgical debulking or extensive metastases removal may also allow for long-term remission in patients with locoregional or isolated resectable distant metastases, or it can palliate symptoms related to tumor mass or catecholamine excess [140]. Systemic chemotherapy and radiotherapy are possible treatment options for patients who are not surgical candidates, although these have only palliative character. However, recent progress in understanding the molecular mechanisms involved in PHEO/PGL development has driven introduction of new promising therapeutic options.

Medical Management and Preparation for Surgery

Immediately after diagnosis, all patients with biochemically active PHEO/PGL should be placed on sufficient adrenoceptor blockade to control symptoms and reduce the risk of hypertensive crises and organ damage mediated by the effects of released catecholamines [6]. There is no consensus regarding the drugs recommended for preoperative management because of wide-ranging practices, international differences in available or approved therapies, and a lack of studies comparing different medications. However, α-adrenoceptor antagonists, calcium-channel blockers, and angiotensin-receptor blockers are recommended [28, 141]. Drugs that can be used in symptom management and presurgical blockade, with suggested doses, are listed in Table 12.8.

If surgery is planned, medication should be introduced at least 7–14 days before the procedure to control blood pressure and heart rate, restore the catecholamine-induced volume depletion, and prevent a surgery-induced catecholamine storm and its consequences [28, 29, 59, 142]. Although there are some speculations regarding the need of preoperative adrenoceptor blockade, the potential benefit of preventing unpredictable

Table 12.8 Drugs used for symptom management and presurgical blockade in patients with PHEO/PGL

Drug	Classification	Suggested dose	Use	Common side effects
α-Adrenoceptor blockers				
Phenoxybenzamine	Long lasting, irreversible, noncompetitive	10 mg 1–3 times daily	First choice for α-adrenoceptor blockade	Orthostatic hypotension, nasal congestion, tachycardia, dizziness
Prazosin	Short acting, specific, competitive	2–5 mg 2–3 times daily	– When phenoxybenzamine is not available – For patients who do not tolerate phenoxybenzamine – For patients with mild hypertension	
Terazosin	Short acting, specific, competitive	2–5 mg daily		
Doxazosin	Short acting, specific, competitive	4–24 mg 2 times daily		
β-Adrenoceptor blockers				
Atenolol	Cardioselective	12.5–25 mg 2–3 times daily	To control tachyarrhythmia resulting from catecholamine excess or from α-adrenoceptor blockade	Fatigue, dizziness, exacerbation of asthma
Metoprolol	Cardioselective	25–50 mg 3–4 times daily		
Propranolol	Nonselective	20–80 mg 1–3 times daily		
Calcium channel blockers				
Amlodipine		10–20 mg daily	– To provide additional control of hypertension for patients on α-adrenoceptor blockers – For patients who do not tolerate α-adrenoceptor blockers – For patients with intermittent hypertension	Headache, edema, dizziness, nausea
Nicardipine		60–90 mg daily		
Nifedipine	Extended-release action	30–90 mg daily		
Verapamil	Extended-release action	180–540 mg daily		
Catecholamine synthesis inhibitors				
Metyrosine		250 mg every 8–12 h for a total dose of 1.5–2 g daily	To provide additional control of hypertension for patients on adrenoceptor blockade	Severe fatigue, sedation, depression, anxiety, galactorrhea, extrapyramidal side effects, nausea

Partially adapted from [6, 8, 141]

instability in blood pressure during surgery is much higher than a relatively low risk of medication-related adverse effects [28]. Preoperative preparation should also include a high-sodium diet and fluid intake to reverse catecholamine-induced blood volume contraction as a prevention of severe hypotension after tumor removal [28].

Alpha-adrenoceptor blockade is usually achieved with oral phenoxybenzamine, which exhibits long-lasting effects that diminishes only after *de novo* α-adrenoceptor synthesis. The initial dose of 10 mg twice daily is titrated upward until symptoms are controlled or side effects appear. Treatment goals are to normalize blood pressure, prevent paroxysmal hypertensive episodes, and eliminate tachyarrhythmias. Side effects of the treatment include orthostatic hypotension, tachycardia, nasal congestion, dry mouth, diplopia, and ejaculatory dysfunction. In patients who do not tolerate phenoxybenzamine, or if the drug is unavailable, other α-blocking agents can be used. These include prazosin, terazosin, or doxazosin. All three agents are short-acting, specific, competitive α_1-adrenergic antagonists, and they also have potential to cause severe postural hypotension [28, 59].

If adequate control of blood pressure and tachyarrhythmias is not achieved by α-blockers, β-blockade is initiated. β-Adrenoceptor blockers should be administered only after adequate pretreatment (at least for 3–4 days) with α-adrenoceptor antagonists to prevent unopposed epinephrine-induced vasoconstriction, which can lead to a hypertensive crisis [13, 141, 143]. Labetalol, which has both α- and β-adrenoceptor antagonistic activities, may also be used in PHEO/PGL patients in doses 200–600 mg twice daily [144]. However, the fixed ratio of α- and β-adrenoceptor blocker (1:4) is often not suitable for patients with PHEO/PGL, and thus, the use of individual α- and β-adrenoceptor antagonists is a better option.

A tyrosine hydroxylase inhibitor, metyrosine, is another valuable medication in management of patients with PHEO/PGL. Metyrosine competitively inhibits tyrosine hydroxylase, resulting in significant depletion of catecholamine production. Thus, metyrosine facilitates control of blood pressure both before and during surgery, especially during the induction of anesthesia and manipulation of the tumor, which can cause both extensive sympathetic activation and catecholamine release. Metyrosine crosses the blood-brain barrier. Therefore, it inhibits catecholamine synthesis not only in the periphery but also in brain and often causes sedation, depression, anxiety, galactorrhea, and, very rarely, extrapyramidal signs. Due to the severity of side effects, the use of metyrosine is reserved for patients with very high levels of catecholamines and those with extensive metastatic disease.

Calcium channel blockers control hypertension and tachyarrhythmias by blocking norepinephrine-mediated calcium influx into vascular smooth muscles. Calcium channel blockers can be used alongside α-adrenoceptor blockers if the blockade is not sufficient. They can replace α-adrenoceptor blockers in patients who are unable to tolerate them [29, 145].

For acute management of hypertensive crisis, either intravenous phentolamine (5 mg every 2 min until adequate control of hypertension or a continuous infusion of 100 mL of phentolamine in 500 mL of 5% dextrose) or sodium nitroprusside (continuous intravenous infusion) is effective. Sometimes, nifedipine (10 mg) administered orally or sublingually can be used to control hypertension. If tachycardia

is present, β-adrenoceptor blockers may be administered. However, they should never be used before α-adrenoceptor blockers, as previously discussed. A list of medications that can precipitate hypertensive episodes in patients with PHEO/PGL is in Table 12.4.

A proposed algorithm for presurgical management of PHEO/PGL patients is shown in Fig. 12.3.

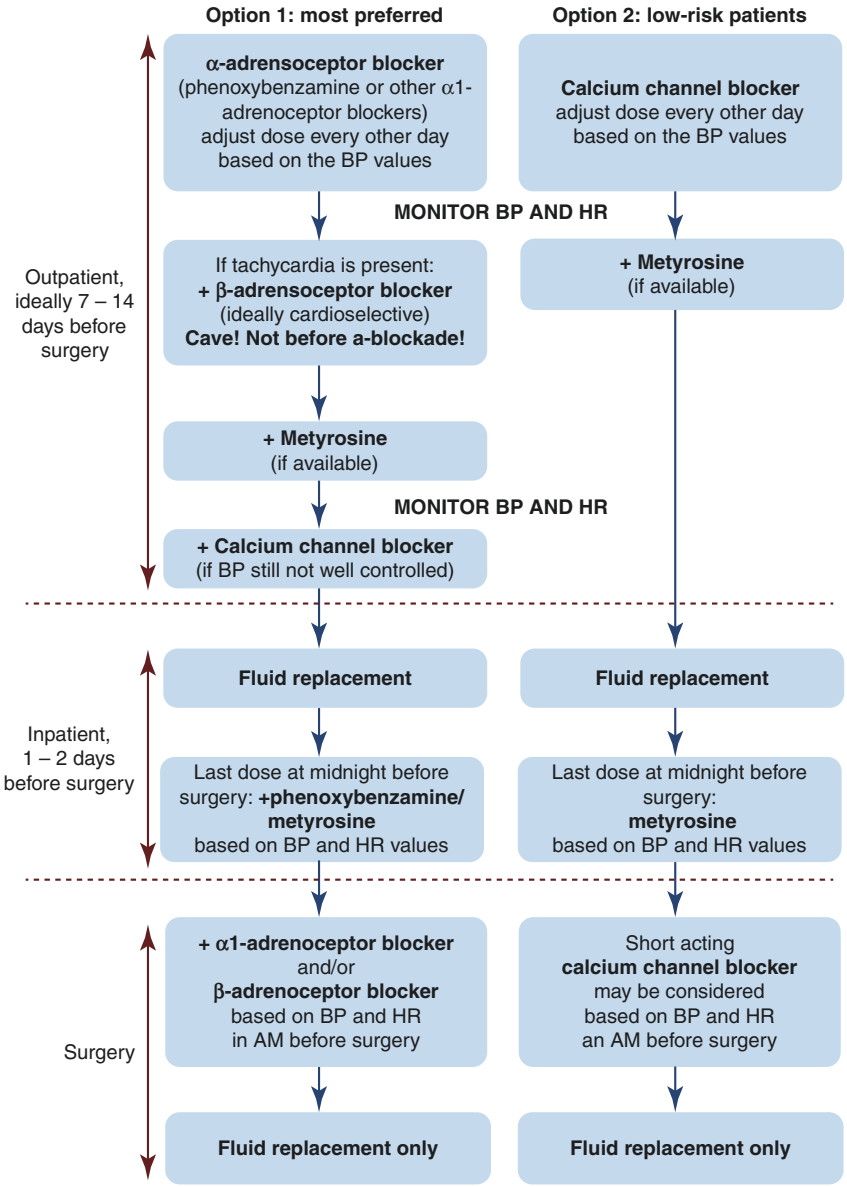

Fig. 12.3 Algorithm for presurgical management of patients with PHEO/PGL [29]. *AM* morning, *BP* blood pressure, *HR* heart rate, *PGL* paraganglioma, *PHEO* pheochromocytoma

Surgical and Perioperative Management

PHEO/PGL surgery requires a multidisciplinary approach and should preferably be performed in centers experienced with PHEO/PGL management and treatment. The current standard for surgical management of adrenal PHEOs is minimally invasive surgery, which can be performed as transperitoneal laparoscopic adrenalectomy or retroperitoneoscopic adrenalectomy [146–148]. For PGLs, open resection is suggested, since they are more likely to be malignant and often arise in areas not accessible for laparoscopy. However, laparoscopic surgery can be used to remove intra-abdominal PGLs smaller than 6 cm [28, 149]. Advantages of laparoscopic approach over an open procedure include lower morbidity, less postoperative pain, and a faster recovery [150]. However, caution should be exercised as the insufflation of carbon dioxide to produce a pneumoperitoneum is associated with iatrogenic acidosis and mechanical compression, which can cause catecholamine release from the tumor [150]. The operation should be converted to an open resection if laparoscopic approach is difficult [28]. For large tumors, laparoscopic surgery may be used, but it requires precise and gentle dissection in order to prevent profuse bleeding, the disruption of the tumor capsule leading to intraoperative dissemination, peritoneal seeding, and recurrence of the tumor [146, 147]. Another method, a single-port robotic adrenalectomy, has been reported as a safe and effective method for both complete and partial resection of PHEO with similar success rates, decreased postoperative pain, and shorter hospitalization, but with higher costs compared to laparoscopic and open surgery [151–153].

In patients with sporadic and hereditary bilateral adrenal PHEOs and in those with small tumors who have undergone a complete resection of a contralateral adrenal gland, a cortical sparing adrenalectomy is recommended [28]. This approach is safe, and if a sufficient amount of adrenal cortex is preserved, it could prevent postoperative adrenal insufficiency and requirements for glucocorticoid and mineralocorticoid replacement [154–156]. Retention of normal glucocorticoid function after cortical sparing partial adrenalectomy is achieved in >50% of patients [157–160]. The risk of recurrence due to residual medullary tissue is reported to be between 0 and 21% [157–159, 161].

In patients with metastatic disease, surgery can be performed for either noncurative debulking or for aggressive resection with the goal of complete remission. Palliative debulking surgery can be performed in some cases for immediate risk reduction and resection of the lesions affecting crucial structures [142, 162]. Surgical debulking can also improve the efficacy of adjuvant therapies by reducing tumor mass and burden [142]. Extensive surgery for metastatic disease can result in successful outcomes and remission in patients with metastases limited to the abdomen [163, 164]. Intraoperative use of gamma probes labeled with radiopharmaceuticals (e.g., ^{123}I-MIBG) can facilitate identification of metastatic sites missed on anatomical imaging [165, 166].

A critical component of intraoperative patient management is avid communication between the surgical and anesthesia teams to anticipate and reduce the likelihood of major hemodynamic events and other complications. The most frequent PHEO/PGL surgery complications include significant changes in blood pressure,

arrhythmias, and hyper- or hypoglycemia. Hypertension surges may occur during induction of anesthesia, intubation, tumor palpation and manipulation, or ligation of tumor vessels. Intraoperative hypertensive crises are managed by administration of intravenous sodium nitroprusside in conjunction with nitroglycerine (to reduce preload), phentolamine, nicardipine, and fenoldopam [29, 167]. Intravenous magnesium sulfate is also used for management of hypertension during PHEO/PGL resection, as it can inhibit catecholamine release from the adrenal medulla, enhance vasodilatation, block catecholamine receptors, and prevent arrhythmias [27, 168]. Severe hypotension may develop following tumor ligation. Hypotension results from a combination of several factors: the loss of catecholamine secretion from tumor, continued α-adrenoceptor blockade, increased systemic capacitance from antihypertensive drugs, contracted plasma volume, surgical bleeding, and anesthetic-induced vasodilation. It may become profound and persistent [27, 167]. In such situations, massive volume resuscitation with saline infusion should be initialized with discontinuation of vasodilators. Vasopressors should be administered only if hypotension persists after plasma expansion to euvolemia. In refractory cases, vasopressin or methylene blue can be utilized. In surgical settings it is important to exclude hemorrhage as a cause of persistent hypotension.

Arrhythmias usually occur during induction or maintenance of general anesthesia. Arrhythmias can be managed with esmolol, propranolol, or lidocaine, but caution is needed when administering these drugs to patients with severe ventricular dysfunction [27].

Hyperglycemia due to increased catecholamine-stimulated glycogenolysis and lipolysis is present in approximately 60% of patients with PHEO/PGL [143]. It is important not to overtreat hyperglycemia as insulin administered during surgical procedure may worsen hypoglycemia after tumor removal or during postoperative period [27]. To prevent hypoglycemia, which often occurs after tumor removal, intravenous glucose replacement (5% dextrose) can be administered.

Postoperative Management

In the postoperative period, patients are at risk for development of complications including hypertension, hypotension, arrhythmias, rebound hypoglycemia, renal dysfunction, or prolonged intubation. Therefore, blood pressure, heart rate, and plasma glucose levels should be closely monitored for 24–48 h after surgery [143]. Moreover, attention has to be paid to patients who underwent a bilateral adrenalectomy, bilateral cortical-sparing adrenalectomy, or unilateral cortical-sparing adrenalectomy of a sole remaining adrenal gland, because of the potential adrenal insufficiency. This requires cautious observation of plasma glucose, electrolytes levels, and endocrine functions.

For postsurgical hypotension, volume replacement is the first-choice treatment. Use of vasopressors may not be effective because of long-acting α-adrenoceptor blockers and catecholamine synthesis inhibitors (metyrosine) used in preoperative

treatment. Often, a high fluid volume is required during the first 24–48 h after surgery (until sympathetic nervous system resumes autoregulation). If hypotension persists regardless of adequate volume replacement, vasopressor agents should be administered [8].

Hypertension after surgery for PHEO/PGL may be caused by volume overload, autonomic instability, or pain. These are treated symptomatically. However, it may also indicate that not all tumor tissue has been resected or that there is a coexistence of essential hypertension.

Biochemical confirmation of remaining tumor should not be done earlier than 5–7 days after surgery to ensure that increases in plasma and urinary catecholamines produced during surgery have dissipated. Ideally, postoperative measurements of metanephrines and 3-methoxytyramine should be obtained 2–6 weeks after surgery. Measurements of 3-methoxytyramine should become commercially available in the near future. Follow-up biochemical screening for recurrent or metastatic disease should be done annually for lifetime or immediately if symptoms reappear [28]. In patients with biochemically silent tumors, annual or biannual imaging studies are performed instead of biochemical testing [169, 170].

Management of Metastatic Pheochromocytoma and Paraganglioma

In PHEO/PGL, there are no known cellular or molecular markers for determining malignancy. Metastatic PHEOs/PGLs are only defined by the presence of metastases at sites where chromaffin cells are not normally present [171]. Metastases can spread via hematogenous or lymphatic pathways, and the most common metastatic sites include lymph nodes, bones, lungs, and liver. In PHEO/PGL patients, metastasis may be present at time of diagnosis or appear months or years later [140]. Frequency of metastases in patients with PHEO/PGL ranges from 1% to 34%. Higher incidence of metastatic disease is associated with certain genetic backgrounds (e.g., mutations in *SDHB* and *FH* genes). Moreover, metastases are more prevalent in PGLs than in PHEOs, ~25% vs. ~10%, respectively [2, 142, 172]. Regardless of the genetic background, patients with PHEO/PGL need to be followed up on a long-term basis, as metastases may occur even 20 years after presentation of a primary tumor.

Clinical manifestation of metastatic PHEO/PGL is similar to benign tumors. Additionally, a patient may present with symptoms related to local invasion of tumors. Some patients may exhibit minimal symptoms or do not have any symptoms at all, despite significantly elevated catecholamine levels. This most likely occurs due to desensitization of adrenoceptors by constantly high catecholamine concentrations.

Biochemical diagnosis and localization of metastatic disease follow the same algorithm as benign PHEOs/PGLs. Metastatic tumors secrete mostly norepinephrine [4, 173, 174], and patients usually have higher levels of plasma and urinary

normetanephrine, which reflects a larger tumor size [175, 176]. Moreover, increased excretion of dopamine and its metabolite, 3-methoxytyramine, is associated with metastatic disease [4, 173, 177]. For localization of metastatic tumors, ^{18}F-FDG PET is more useful than specific positron-emitting compounds or ^{123}I-MIBG scintigraphy, because of dedifferentiation of the tumor and loss of expression of cell membrane and vesicular transporter systems [8, 101], as discussed in the tumor localization section.

Management of metastatic PHEO/PGL is a challenging task and requires a multidisciplinary approach. Currently, there is no effective treatment for metastatic PHEO/PGL. The aim of planned treatment interventions is an attempt for definitive cure of limited disease and palliation for advanced disease. In patients with slowly progressive disease, a wait-and-watch strategy can be applied with regular biochemical and radiological follow-ups. Each step in treatment should be individualized to the patient's needs and intended therapeutic goals. An active therapeutic intervention is needed in the presence of uncontrolled hormone- or tumor-related symptoms or high tumor burden as defined by RECIST criteria (seven or more bone metastases, replacement of >50% of the liver parenchyma, multiple pulmonary nodules >2 cm, or significant radiologic progression) [178, 179]. Besides pharmacotherapy of hypertension and other symptoms and surgical debulking, current treatment options for metastatic PHEO/PGL include local ablative therapies, radiotherapy, and chemotherapy (Fig. 12.4). Novel molecular-targeted therapies are under development and may be introduced in the near future.

Targeted Radiotherapy

^{131}I-MIBG therapy is a systemic targeted radiotherapy used in patients with inoperable metastatic disease and positive uptake on ^{123}I-MIBG scintigraphy. Treatment can be administered as a single dose (50–900 mCi) or as multiple doses (100–300 mCi) at intervals of 3–6 months, with a total dose limit of 1000 mCi [181, 182]. Higher doses are associated with serious hematologic and non-hematologic toxicity [182]. However, when multiple doses of low to intermediate ^{131}I-MIBG activities (50–350 mCi) are administered, treatment is well tolerated, with minimal toxicity, which includes mild bone marrow suppression, mildly elevated liver enzymes, some renal toxicity, and hypothyroidism. Around 30% of patients show partial response (<50% reduction of tumor mass). Complete response is low, 0–18%. Nevertheless, a significant number of patients report symptomatic and biochemical responses [182, 183].

Before treatment administration, several precautions must be taken: (a) patients should be on antihypertensive drugs that do not interfere with ^{131}I-MIBG uptake (phenoxybenzamine, nifedipine, atenolol), and all interfering drugs (Table 12.7) have to be discontinued before therapy; (b) 24–48 h prior to therapy and 10–15 days after therapy, patients have to take potassium iodine, saturated solution of potassium iodide, Lugol's solution, or potassium perchlorate to protect the thyroid from accumulation of radioiodine; (c) because of the hematologic, liver, and renal toxicity of ^{131}I-MIBG, the patient's hematopoietic parameters, liver, and renal function should be adequate [8, 182].

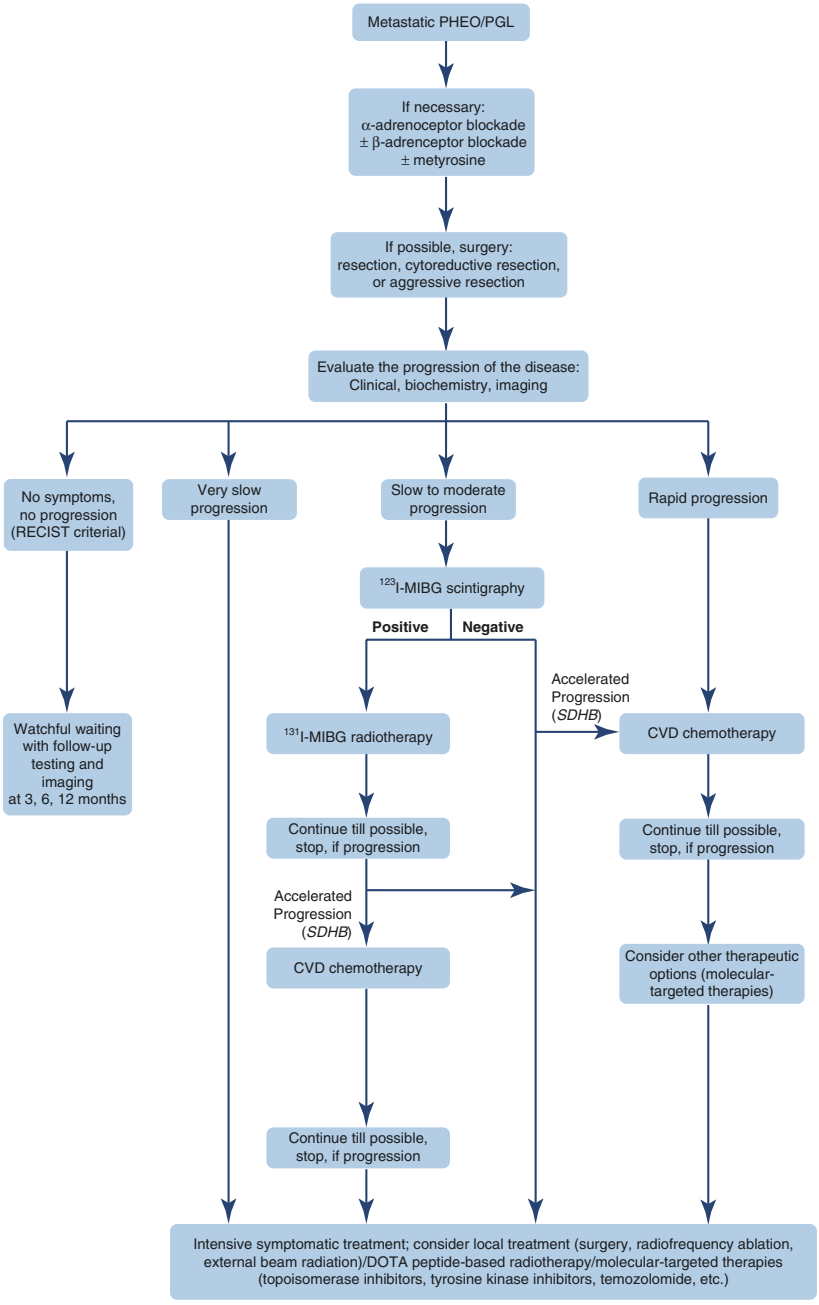

Fig. 12.4 Algorithm for management of metastatic PHEO/PGL [8, 180]. *CVD* cyclophosphamide, vincristine, and dacarbazine, *MIBG* metaiodobenzylguanidine, *PGL* paraganglioma, *PHEO* pheochromocytoma, *RECIST* response evaluation criteria in solid tumors, *SDHB* succinate dehydrogenase subunit B

Another promising targeted radiotherapy treatment is represented by radionuclide-labeled DOTA peptide-based therapy (DOTATATE, DOTATOC, DOTANOC), which targets somatostatin receptors and uses the long-acting, somatostatin analogue octreotide (TATE, TOC, NOC) conjugated with radionuclide-labeled DOTA (lutetium, ^{177}Lu; yttrium, ^{90}Y; or indium, ^{111}In). Since many PHEOs/PGLs express somatostatin receptors, treatment can be used in patients with positive octreoscan or ^{68}Ga-DOTATATE imaging [184–191].

Radiofrequency Ablation and External Beam Radiation

Percutaneous radiofrequency ablation (RFA) is a safe and minimally invasive treatment modality aimed at growth inhibition and control. It is used for management of painful metastasis and symptoms related to catecholamine excess. RFA has been shown to be particularly effective in the treatment of osseous and liver lesions, which are successfully ablated without recurrence [192–195].

In the past, use of external beam radiation therapy (EBRT) in PHEO/PGL treatment has been controversial, since metastatic PHEOs/PGLs were considered to be resistant to radiation. However, recent data suggests that EBRT can be used as adjuvant treatment to chemotherapy and systemic radiotherapy for local control of bulky metastases, especially with osseous lesions. EBRT seems to be effective in symptomatic control of disease in patients with a limited burden of metastases. Moreover, it is also becoming accepted as a first-line therapy for head and neck PGLs [196–198]. Head and neck PGLs are often localized in inaccessible areas or are extremely adherent to adjacent structures. Therefore, surgical resection cannot be performed, or it would result in devastating postoperative morbidity related to dysfunction of cranial nerves [199]. Radiotherapeutic options for the treatment of non-resectable head and neck tumors include the traditional fractionated EBRT or radiosurgery using Gamma Knife, linear accelerator (LINAC), or CyberKnife. Development of stereotactic radiosurgery allows for delivery of high doses of radiation with more precise targeting and a decreased toxicity in the surrounding tissue [200]. Several studies have shown successful tumor control (stabilization or regression of tumor volumes) along with symptomatic improvement in more than 95% of patients with glomus jugulare tumors [201–203].

Systemic Chemotherapy

Systemic chemotherapy is recommended for rapidly progressive inoperable metastatic PHEOs/PGLs and for patients with a high tumor burden or a large number of bone metastases. In such cases, it primarily serves as a palliative treatment option, improving patient's quality of life. In addition, it may also serve as a neoadjuvant therapy to improve chances of successful surgical treatment of large tumors.

Although there is not a chemotherapy combination or single treatment that would have long-term efficacy in metastatic PHEO/PGL, some of the used regimens can stabilize disease for several years. The combination of cyclophosphamide, vincristine, and dacarbazine (CVD), administered intravenously in 21-day cycles, is the

most extensively used for PHEO/PGL. This approach yields complete or partial response rates of 57% [180, 204]. Moreover, 79% of treated patients had a complete or partial biochemical response and showed objective improvement in performance status and clinical findings [204]. Effectiveness of CVD chemotherapy might be evident within 1–3 months after initiation of treatment. In responders, chemotherapy should be continued, although the evidence of increased overall survival is conflicting [205–208]. CVD chemotherapy has been found to be particularly beneficial in patients with mutations in the *SDHB* gene [209].

There is anecdotal evidence of successful treatment of individual cases using alternative chemotherapeutic agents alone or in combination, including temozolomide; cyclophosphamide and methotrexate, thalidomide, ifosfamide, etoposide, carboplatin, vincristine, cyclophosphamide, and doxorubicin; and cisplatin and 5-fluorouracil [206, 210–213].

Molecular-Targeted Therapies

Recently, progress in the understanding of pathophysiological mechanisms involved in development of PHEO/PGL was made, especially due to the identification of disease susceptibility genes. These discoveries allowed for identification of dysfunction of several critical signaling pathways and, thus, potential novel treatment targets.

For instance, the hypoxia-inducible factor (HIF) signaling pathway has been found to be activated in certain PHEOs/PGLs due to mutations in genes encoding Krebs cycle enzymes (*SDHx*, *FH*, *IDH*, *MDH2*), mutations in *HIF2A* gene, or upstream regulators of HIF signaling, reviewed in [214, 215]. Moreover, gene expression studies revealed an increased expression of hypoxia-angiogenic pathway components, e.g., vascular endothelial growth factors (VEGFs) and other growth factors. Therefore, inhibiting or modifying metabolic processes and enzymes participating in metabolic reprogramming poses a promising therapeutic strategy. Potential molecular/metabolic therapeutic targets are listed in Table 12.9.

Table 12.9 Potential molecular/metabolic therapeutic targets in PHEO/PGL

Therapeutic target	Treatment effects	Examples of agents
HIF signaling (reviewed in [216–218])		
HIF-α mRNA/protein expression	Inhibition of HIF-α mRNA or protein expression resulting in decreased HIF-α accumulation and activation	Wortmannin, LY94002, GFC-0941, PI-103, rapamycin, PP242, aminoflavone, glyceollins, topotecan, EZN-2968, 2ME2, ENMD-1198, geldanamycin and analogues, vorinostat, YC-1, PX-478, PX-12, cardiac glycosides, FM19G11, HIF-2α translational inhibitors
HIF-α dimerization	Inhibition of HIF-α/HIF-1β dimerization	Acriflavine, PT2385

(continued)

Table 12.9 (continued)

Therapeutic target	Treatment effects	Examples of agents
HIF binding to DNA	Inhibition of HIF dimers binding to DNA	Echinomycin, polyamides
HIF transcriptional activity	Inhibition of transcription of HIF target genes	Chetomin, bortezomib, amphotericin B, triptolide, AJM290, AW464
Hypoxia	Apoptosis of hypoxic cell	Hypoxia-activated prodrugs: TH-302, EO9, AQ4N, PR-104, tirapazamine, SN30000, TH-4000
Angiogenesis	VEGF, VEGFR inhibition	Sunitinib, sorafenib, pazopanib, bevacizumab
Glycolysis (reviewed in [217, 219])		
Glucose uptake	Inhibition of glucose transport	GLUTs inhibitors: flavonoids (phloretin, silybin), STF-31, WZB117, ritonavir
HK 1/2	Inhibition	3-Bromopyruvate 2-deoxyglucose, lonidamine
PDK1	Inhibition (to allow activity of PDH)	Dichloroacetate
PFKB3	Inhibition	3PO
LDHA	Inhibition	shRNA, gossypol/AT-101 and derivatives, galloflavin
PKM2	Induction of apoptosis	Somatostatin and its derivatives, TLN-232/CAP-232
MCTs	Inhibition of lactate transport	AZD3965 MCT1/2 specific inhibitors, CHC, phenylpyruvate, bioflavonoids
Glutaminolysis (reviewed in [220])		
Glutamine uptake	Glutamine transporters inhibition	BCH, GPNA, benzylserine
Glutaminase	Inhibition	BPTES/CB-839, compound 968
GOT2/GPT2	Inhibition	Aminooxyacetate
GDH1	Inhibition	Purpurin/R162, EGCG
Fatty acid and lipid synthesis (reviewed in [221–223])		
ACLY	Inhibition	SB-204990
Acyl-CoA synthetase	Inhibition	
Acetyl-CoA carboxylase	Inhibition, induction of apoptosis/autophagy	Soraphen A
Fatty acid synthase	Inhibition, induction of apoptosis	Cerulenin, C75, flavonoids
Choline kinase	Inhibition	MN58b
Phospholipid metabolism	Inhibition	Metformin
Dysfunctional Krebs cycle enzymes and metabolites (reviewed in [217, 224])		
IDH1/2	Inhibition of IDH mutants, inhibition of 2HG production	Mutant IDH inhibitors

Table 12.9 (continued)

Therapeutic target	Treatment effects	Examples of agents
α-Ketoglutarate-dependent dioxygenases	Restoring the function	α-Ketoglutarate analogues
Low citrate	Increase in citrate levels, inhibition of PFK, arrest of glycolysis, induction of apoptosis	Citrate [225]
Proton extrusion (reviewed in [217, 221])		
Na+/H+ exchanger	Inhibition	Cariporide, amiloride
Bicarbonate/Cl- exchanger	Inhibition	S3705
MCT1 lactate/H+ symporter	Inhibition	α-Cyano-4-OH-cinnamate
Carbonic anhydrases 9 and 12	Inhibition	Sulfonamide indisulam
F1F0 ATP synthase	Inhibition	Angiostatin
V-ATPase	Inhibition	Bafilomycin A1
Other (reviewed in [221])		
DNA methylation	Inhibition of methylation	DNA demethylating agents: decitabine [216]
AMPK	Activation	Biguanides, thiazolidinediones, bevacizumab, erlotinib
LAT1	Inhibition of amino acid transport	2-Aminocyclo (2.2.1)-heptane 2-carboxylic acid
SIRT1	Stimulation of SIRT1-dependent deacetylation PGC1α	Resveratrol
ROS	Neutralizing ROS by antioxidants to reduce HIF-α activation	N-Acetylcysteine, vitamin C
ROS	Induction of ROS overproduction	Menadione, gadolinium texaphyrin, β-lapachone
Antioxidant systems (GSH)	Inhibition to achieve ROS accumulation	Buthionine sulfoximine, isothiocyanates, mangafodipir

Adapted from [226]

3PO 3-(3-pyridinyl)-1-(4-pyridinyl)-2-propen-1-on; *Acetyl-CoA* acetyl coenzyme A, *ACLY* ATP citrate lyase, *AMPK* AMP-activated protein kinase, *ATP* adenosine triphosphate, *BCH* 2-aminobicyclo(2,2,1)-heptane-2-carboxylic acid, *BPTES* bis-2-[5-phenylacetamido-1,2,4-thiadiazol-2-yl]ethyl sulfide, *CHC* α-cyano-4-hydroxycinnamate, *EGCG* epigallocatechin gallate, *GDH1* glutamate dehydrogenase 1, *GLUT* glucose transporter, *GOT2* glutamate oxaloacetate transaminase 2, *GPNA* γ-L-glutamyl-p-nitroanilide, *GPT2* glutamate pyruvate transaminase 2, *HIF* hypoxia-inducible factor, *HK* hexokinase, *IDH* isocitrate dehydrogenase, *LAT1* L-type amino acid transporter 1, *LDHA* lactate dehydrogenase A, *MCT* monocarboxylate transporter, *PDH* pyruvate dehydrogenase, *PFK* phosphofructokinase, *mRNA* messenger RNA, *PGC1α* peroxisome proliferator-activated receptor-γ co-activator 1α, *PHD* prolyl hydroxylase domain-containing protein, *PKM2* pyruvate kinase, isoenzyme 2, *ROS* reactive oxygen species, *SDH* succinate dehydrogenase, *SIRT1* sirtuin 1

One of the approaches is to modify/interrupt the HIF signaling pathway, and several possible strategies are being tested. For example, drugs inhibiting HIF mRNA or protein expression (such as antiangiogenic agents, drugs targeting PI3K/Akt/mTOR pathway, or heat shock protein 90 activity inhibitors). A few years ago, sunitinib, a tyrosine kinase inhibitor preventing angiogenesis through targeting the VEGF receptors, was introduced. In vitro studies have suggested that sunitinib induces apoptosis in rat PHEO cells and directly inhibits catecholamine synthesis by reducing the activity of tyrosine hydroxylase [227, 228]. However, when used in clinical settings, the results were conflicting [229–232]. Another compound, everolimus, targeting the mTOR pathway, was evaluated in a small number of patients with PHEO/PGL with disappointing results [233, 234]. However, there are current clinical trials evaluating the effects of combination therapy with mTOR and PI3K inhibitors in other cancers, which may show more significant results [235, 236].

Inhibition of HIF dimerization, which is one of the steps leading to HIF-α activation, and inhibition of HIF binding to DNA are other possible therapeutic targets [237], reviewed in [215, 218].

Cancer cell metabolism depends on glucose and glutamine. Therefore, altering the uptake of these nutrients by glucose transporters inhibitors, inhibitors of glycolytic enzymes, or inhibitors of glutaminolysis may be another promising treatment approach, reviewed in [219, 220, 238, 239].

Other options for targeted PHEO/PGL therapy include restoration of the enzymatic activity of nonfunctioning Krebs cycle enzymes, replenishment of depleted substrates for the cell, and inhibition of overexpressed enzymes. Therapeutic agents are under development, which include small molecule inhibitors of certain proteins or agents restoring functionality of Krebs cycle enzymes, reviewed in [215]. In *SDHB*-deficient cells, the use of proteostasis regulators (e.g., histone deacetylase inhibitors) leads to an increase in the total amount of SDHB protein in cell [240].

Tumors driven by *VHL* mutations display promoter hypermethylation of a few target genes and a prevalent hypomethylation outside CpG islands. *SDH*- and *FH*-mutated PHEOs/PGLs are characterized by the hypermethylator phenotype [241], suggesting the use of demethylating agents in the treatment of PHEO/PGL [216].

Although molecular therapies for PHEO/PGL are still under development, a deeper understanding of the molecular mechanisms associated with tumorigenesis facilitates identification of novel treatment targets and, in the near future, may help to improve outcomes of patients with metastatic PHEO/PGL.

Conflict of Interest Declaration The authors declare that they have no conflict of interest.

References

1. DeLellis RA, Lloyd RV, Heitz PU, Eng C. Pathology and genetics of tumours of endocrine organs., World Health Organization classification of tumours, vol. 8. Lyon: IARC Press; 2004.
2. Ayala-Ramirez M, Feng L, Johnson MM, Ejaz S, Habra MA, Rich T, Busaidy N, et al. Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. J Clin Endocrinol Metab. 2011;96(3):717–25. doi:10.1210/jc.2010-1946.
3. Brouwers FM, Eisenhofer G, Tao JJ, Kant JA, Adams KT, Linehan WM, Pacak K. High frequency of SDHB germline mutations in patients with malignant catecholamine-producing paragangliomas: implications for genetic testing. J Clin Endocrinol Metab. 2006;91(11):4505–9. doi:10.1210/jc.2006-0423.
4. Eisenhofer G, Lenders JW, Siegert G, Bornstein SR, Friberg P, Milosevic D, Mannelli M, et al. Plasma methoxytyramine: a novel biomarker of metastatic pheochromocytoma and paraganglioma in relation to established risk factors of tumour size, location and SDHB mutation status. Eur J Cancer. 2012;48(11):1739–49. doi:10.1016/j.ejca.2011.07.016.
5. McNeil AR, Blok BH, Koelmeyer TD, Burke MP, Hilton JM. Phaeochromocytomas discovered during coronial autopsies in Sydney, Melbourne and Auckland. Aust NZ J Med. 2000;30(6):648–52.
6. Martucci VL, Pacak K. Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. Curr Probl Cancer. 2014;38(1):7–41. doi:10.1016/j.currproblcancer.2014.01.001.
7. Pacak K, Lenders JWM, Eisenhofer G. Pheochromocytoma. Diagnosis, localization, and treatment. Malden, MA: Blackwell Publishing, Inc.; 2007.
8. Pacak K, Timmers HJLM, Eisenhofer G. Pheochromocytoma. In: Jameson JL, DeGroot LJ, De Kretser DM, Giudice L, Grossman A, Melmed S, Potts JT, Weir GC, editors. Endocrinology: Adult & pediatric. Philadelphia, PA: Elsevier/Saunders; 2016. p. 1902–1930. e1906.
9. Plouin PF, Degoulet P, Tugaye A, Ducrocq MB, Menard J. Screening for phaeochromocytoma: in which hypertensive patients? A semiological study of 2585 patients, including 11 with phaeochromocytoma (author's transl). Nouv Press Med. 1981;10(11):869–72.
10. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet. 2005;366(9486):665–75. doi: 10.1016/S0140-6736(05)67139-5.
11. Reisch N, Peczkowska M, Januszewicz A, Neumann HP. Pheochromocytoma: presentation, diagnosis and treatment. J Hypertens. 2006;24(12):2331–9. doi: 10.1097/01.hjh.0000251887.01885.54.
12. Kantorovich V, Pacak K. Pheochromocytoma hypertensive crisis. In: Loriaux L, editor. Endocrine emergencies. Recognition and treatment. New York, NY: Humana Press; 2014. p. 139–47.
13. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev. 2003;24(4):539–53. doi: 10.1210/er.2002-0013.
14. van der Harst E, de Herder WW, de Krijger RR, Bruining HA, Bonjer HJ, Lamberts SW, van den Meiracker AH, Stijnen TH, Boomsma F. The value of plasma markers for the clinical behaviour of phaeochromocytomas. Eur J Endocrinol. 2002;147(1):85–94.
15. Mannelli M, Lenders JW, Pacak K, Parenti G, Eisenhofer G. Subclinical phaeochromocytoma. Best Pract Res Clin Endocrinol Metab. 2012;26(4):507–15. doi:10.1016/j.beem.2011.10.008.
16. Brouwers FM, Eisenhofer G, Lenders JW, Pacak K. Emergencies caused by pheochromocytoma, neuroblastoma, or ganglioneuroma. Endocrinol Metab Clin N Am. 2006;35(4):699–724. viii. doi: 10.1016/j.ecl.2006.09.014.

17. Brouwers FM, Lenders JW, Eisenhofer G, Pacak K. Pheochromocytoma as an endocrine emergency. Rev Endocr Metab Disord. 2003;4(2):121–8.
18. Baguet JP, Hammer L, Mazzuco TL, Chabre O, Mallion JM, Sturm N, Chaffanjon P. Circumstances of discovery of phaeochromocytoma: a retrospective study of 41 consecutive patients. Eur J Endocrinol. 2004;150(5):681–6.
19. Mannelli M, Ianni L, Cilotti A, Conti A. Pheochromocytoma in Italy: a multicentric retrospective study. Eur J Endocrinol. 1999;141(6):619–24.
20. Manger WM, Gifford RW. Pheochromocytoma. J Clin Hypertens. 2002;4(1):62–72.
21. Zelinka T, Strauch B, Pecen L, Widimsky J Jr. Diurnal blood pressure variation in pheochromocytoma, primary aldosteronism and Cushing's syndrome. J Hum Hypertens. 2004;18(2):107–11. doi: 10.1038/sj.jhh.1001644.
22. Zelinka T, Strauch B, Petrak O, Holaj R, Vrankova A, Weisserova H, Pacak K, Widimsky J Jr. Increased blood pressure variability in pheochromocytoma compared to essential hypertension patients. J Hypertens. 2005;23(11):2033–9.
23. Levenson JA, Safar ME, London GM, Simon AC. Haemodynamics in patients with phaeochromocytoma. Clin Sci (Lond). 1980;58(5):349–56.
24. Giavarini A, Chedid A, Bobrie G, Plouin PF, Hagege A, Amar L. Acute catecholamine cardiomyopathy in patients with phaeochromocytoma or functional paraganglioma. Heart. 2013;99(19):1438–44. doi:10.1136/heartjnl-2013-304073.
25. Tagawa M, Nanba H, Suzuki H, Nakamura Y, Uchiyama H, Ochiai S, Terunuma M, Yahata K, Minamino T. Ventricular rhythm and hypotension in a patient with pheochromocytoma-induced myocardial damage and reverse takotsubo cardiomyopathy. Intern Med. 2015;54(18):2343–9. doi:10.2169/internalmedicine.54.4732.
26. Wu XM, Chen JJ, Wu CK, Lin LY, Tseng CD. Pheochromocytoma presenting as acute myocarditis with cardiogenic shock in two cases. Intern Med. 2008;47(24):2151–5.
27. Hodin R, Lubitz C, Phitayakorn R, Stephen A. Diagnosis and management of pheochromocytoma. Curr Probl Surg. 2014;51(4):151–87. doi:10.1067/j.cpsurg.2013.12.001.
28. Lenders, J. W., Q. Y. Duh, G. Eisenhofer, A. P. Gimenez-Roqueplo, S. K. Grebe, M. H. Murad, M. Naruse, K. Pacak, W. F. Young, Jr., and Society Endocrine. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–42. doi:10.1210/jc.2014-1498.
29. Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab. 2007;92(11):4069–79. doi: 10.1210/jc.2007-1720.
30. Barancik M. Inadvertent diagnosis of pheochromocytoma after endoscopic premedication. Dig Dis Sci. 1989;34(1):136–8.
31. Bittar DA. Innovar-induced hypertensive crises in patients with pheochromocytoma. Anesthesiology. 1979;50(4):366–9.
32. Cook RF, Katritsis D. Hypertensive crisis precipitated by a monoamine oxidase inhibitor in a patient with phaeochromocytoma. BMJ. 1990;300(6724):614.
33. Jan T, Metzger BE, Baumann G. Epinephrine-producing pheochromocytoma with hypertensive crisis after corticotropin injection. Am J Med. 1990;89(6):824–5.
34. Manger WM, Gifford RW Jr. Pheochromocytoma: current diagnosis and management. Cleve Clin J Med. 1993;60(5):365–78.
35. Bravo EL, Gifford RW Jr. Pheochromocytoma. Endocrinol Metab Clin N Am. 1993;22(2):329–41.
36. Ionescu CN, Sakharova OV, Harwood MD, Caracciolo EA, Schoenfeld MH, Donohue TJ. Cyclic rapid fluctuation of hypertension and hypotension in pheochromocytoma. J Clin Hypertens (Greenwich). 2008;10(12):936–40. doi:10.1111/j.1751-7176.2008.00046.x.
37. Ueda T, Oka N, Matsumoto A, Miyazaki H, Ohmura H, Kikuchi T, Nakayama M, Kato S, Imaizumi T. Pheochromocytoma presenting as recurrent hypotension and syncope. Intern Med. 2005;44(3):222–7.
38. Bouloux PG, Fakeeh M. Investigation of phaeochromocytoma. Clin Endocrinol. 1995;43(6):657–64.
39. Fung MM, Viveros OH, O'Connor DT. Diseases of the adrenal medulla. Acta Physiol (Oxford). 2008;192(2):325–35. doi:10.1111/j.1748-1716.2007.01809.x.

40. Gifford RW Jr, Bravo EL, Manger WM. Diagnosis and management of pheochromocytoma. Cardiology. 1985;72(Suppl 1):126–30.
41. Adlan MA, Bondugulapati LN, Premawardhana LD. Glucose intolerance and diabetes mellitus in endocrine disorders—two case reports and a review. Curr Diabetes Rev. 2010;6(5):266–73.
42. Bravo EL. Evolving concepts in the pathophysiology, diagnosis, and treatment of pheochromocytoma. Endocr Rev. 1994;15(3):356–68.
43. Chiasson JL, Shikama H, Chu DT, Exton JH. Inhibitory effect of epinephrine on insulin-stimulated glucose uptake by rat skeletal muscle. J Clin Investig. 1981;68(3):706–13.
44. Colwell JA. Inhibition of insulin secretion by catecholamines in pheochromocytoma. Ann Intern Med. 1969;71(2):251–6.
45. Hamaji M. Pancreatic alpha- and beta-cell function in pheochromocytoma. J Clin Endocrinol Metab. 1979;49(3):322–5.
46. La Batide-Alanore A, Chatellier G, Plouin PF. Diabetes as a marker of pheochromocytoma in hypertensive patients. J Hypertens. 2003;21(9):1703–7.
47. Rosen SG, Clutter WE, Shah SD, Miller JP, Bier DM, Cryer PE. Direct alpha-adrenergic stimulation of hepatic glucose production in human subjects. Am J Phys. 1983;245(6):E616–26.
48. Viale G, Dell'Orto P, Moro E, Cozzaglio L, Coggi G. Vasoactive intestinal polypeptide-, somatostatin-, and calcitonin- producing adrenal pheochromocytoma associated with the watery diarrhea (WDHH) syndrome. First case report with immunohistochemical findings. Cancer. 1985;55(5):1099–106.
49. Callender GG, Rich T, Lee JE, Perrier ND, Grubbs EG. Pheochromocytoma. In: Yao JC, Hoff PM, Hoff AO, editors. Neuroendocrine tumors. New York, NY: Humana Press; 2011. p. 221–43.
50. Jochmanova I, Zelinka T, Widimsky J Jr, Pacak K. HIF signaling pathway in pheochromocytoma and other neuroendocrine tumors. Physiol Res. 2014;63(Suppl 2):S251–62.
51. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med. 2001;134(4):315–29.
52. Eisenhofer G, Goldstein DS, Kopin IJ, Crout JR. Pheochromocytoma: rediscovery as a catecholamine-metabolizing tumor. Endocr Pathol. 2003;14:193–212.
53. Eisenhofer G, Lenders JWM, Pacak K. Biochemical diagnosis of pheochromocytoma. In: Lehnert H, editor. Pheochromocytoma. Pathophysiology and clinical management. Basel, Switzerland: Karger; 2004. p. 76–106.
54. Eisenhofer G, Lenders JW, Linehan WM, Walther MM, Goldstein DS, Keiser HR. Plasma normetanephrine and metanephrine for detecting pheochromocytoma in von Hippel-Lindau disease and multiple endocrine neoplasia type 2. N Engl J Med. 1999;340:1872–9.
55. Eisenhofer G, Peitzsch M. Laboratory evaluation of pheochromocytoma and paraganglioma. Clin Chem. 2014;60(12):1486–99. doi:10.1373/clinchem.2014.224832.
56. Hickman PE, Leong M, Chang J, Wilson SR, McWhinney B. Plasma free metanephrines are superior to urine and plasma catecholamines and urine catecholamine metabolites for the investigation of phaeochromocytoma. Pathology. 2009;41(2):173–7. doi:10.1080/00313020802579284.
57. Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, Keiser HR, Goldstein DS, Eisenhofer G. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA. 2002;287(11):1427–34.
58. Mullins F, O'Shea P, FitzGerald R, Tormey W. Enzyme-linked immunoassay for plasma-free metanephrines in the biochemical diagnosis of phaeochromocytoma in adults is not ideal. Clin Chem Lab Med. 2012;50(1):105–10. doi:10.1515/CCLM.2011.742.
59. Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB, Kimura N, et al. Pheochromocytoma: recommendations for clinical practice from the First International Symposium October 2005. Nat Clin Pract Endocrinol Metab. 2007;3(2):92–102. doi:10.1038/ncpendmet0396.
60. Raber W, Raffesberg W, Bischof M, Scheuba C, Niederle B, Gasic S, Waldhausl W, Roden M. Diagnostic efficacy of unconjugated plasma metanephrines for the detection of pheochromocytoma. Arch Intern Med. 2000;160(19):2957–63.

61. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab. 2003;88(2):553–8. doi: 10.1210/jc.2002-021251.
62. Unger N, Pitt C, Schmidt IL, Walz MK, Schmid KW, Philipp T, Mann K, Petersenn S. Diagnostic value of various biochemical parameters for the diagnosis of pheochromocytoma in patients with adrenal mass. Eur J Endocrinol. 2006;154(3):409–17. doi: 10.1530/eje.1.02097.
63. Vaclavik J, Stejskal D, Lacnak B, Lazarova M, Jedelsky L, Kadalova L, Janosova M, Frysak Z, Vlcek P. Free plasma metanephrines as a screening test for pheochromocytoma in low-risk patients. J Hypertens. 2007;25(7):1427–31. doi:10.1097/HJH.0b013e32813aeb5a. 00004872-200707000-00019 [pii]
64. Boyle JG, Davidson DF, Perry CG, Connell JM. Comparison of diagnostic accuracy of urinary free metanephrines, vanillyl mandelic Acid, and catecholamines and plasma catecholamines for diagnosis of pheochromocytoma. J Clin Endocrinol Metab. 2007;92(12):4602–8. doi:10.1210/jc.2005-2668.
65. Peitzsch M, Prejbisz A, Kroiss M, Beuschlein F, Arlt W, Januszewicz A, Siegert G, Eisenhofer G. Analysis of plasma 3-methoxytyramine, normetanephrine and metanephrine by ultraperformance liquid chromatography-tandem mass spectrometry: utility for diagnosis of dopamine-producing metastatic phaeochromocytoma. Ann Clin Biochem. 2013;50(Pt 2):147–55. doi:10.1258/acb.2012.012112.
66. Bravo EL, Tarazi RC, Fouad FM, Vidt DG, Gifford RW Jr. Clonidine-suppression test: a useful aid in the diagnosis of pheochromocytoma. N Engl J Med. 1981;305(11):623–6.
67. Eisenhofer G, Goldstein DS, Walther MM, Friberg P, Lenders JW, Keiser HR, Pacak K. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. J Clin Endocrinol Metab. 2003;88(6):2656–66. doi: 10.1210/jc.2002-030005.
68. Eisenhofer G, Goldstein DS, Sullivan P, Csako G, Brouwers FM, Lai EW, Adams KT, Pacak K. Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. J Clin Endocrinol Metab. 2005;90:2086–75. doi: 10.1210/jc.2004-2025.
69. Poirier E, Thauvette D, Hogue JC. Management of exclusively dopamine-secreting abdominal pheochromocytomas. J Am Coll Surg. 2013;216(2):340–6. doi:10.1016/j.jamcollsurg.2012.10.002.
70. Eiden LE, Iacangelo A, Hsu CM, Hotchkiss AJ, Bader MF, Aunis D. Chromogranin A synthesis and secretion in chromaffin cells. J Neurochem. 1987;49(1):65–74.
71. Grossrubatscher E, Dalino P, Vignati F, Gambacorta M, Pugliese R, Boniardi M, Rossetti O, Marocchi A, Bertuzzi M, Loli P. The role of chromogranin A in the management of patients with phaeochromocytoma. Clin Endocrinol. 2006;65(3):287–93. doi:10.1111/j.1365-2265.2006.02591.x.
72. Zuber S, Wesley R, Prodanov T, Eisenhofer G, Pacak K, Kantorovich V. Clinical utility of chromogranin A in SDHx-related paragangliomas. Eur J Clin Investig. 2014;44(4):365–71. doi:10.1111/eci.12245.
73. Cleary S, Phillips JK, Huynh TT, Pacak K, Fliedner S, Elkahloun AG, Munson P, Worrell RA, Eisenhofer G. Chromogranin a expression in phaeochromocytomas associated with von Hippel-Lindau syndrome and multiple endocrine neoplasia type 2. Horm Metab Res. 2007;39(12):876–83. doi:10.1055/s-2007-993135.
74. d'Herbomez M, Do Cao C, Vezzosi D, Borzon-Chasot F, Baudin E, endocrines groupe des tumeurs. Chromogranin A assay in clinical practice. Ann Endocrinol (Paris). 2010;71(4):274–80. doi:10.1016/j.ando.2010.04.004.
75. Berenyi MR, Singh G, Gloster ES, Davidson MI, Woldenberg DH. ACTH-producing pheochromocytoma. Arch Pathol Lab Med. 1977;101(1):31–5.
76. Kumar M, Kumar V, Talukdar B, Mohta A, Khurana N. Cushing syndrome in an infant due to cortisol secreting adrenal pheochromocytoma: a rare association. J Pediatr Endocrinol Metab. 2010;23(6):621–5.
77. Nijhoff MF, Dekkers OM, Vleming LJ, Smit JW, Romijn JA, Pereira AM. ACTH-producing pheochromocytoma: clinical considerations and concise review of the literature. Eur J Intern Med. 2009;20(7):682–5. doi:10.1016/j.ejim.2009.08.002.

78. Eisenhofer G. Editorial: biochemical diagnosis of pheochromocytoma—is it time to switch to plasma-free metanephrines? J Clin Endocrinol Metab. 2003;88(2):550–2.
79. Lenders JW, Willemsen JJ, Eisenhofer G, Ross HA, Pacak K, Timmers HJ, Sweep CG. Is supine rest necessary before blood sampling for plasma metanephrines? Clin Chem. 2007;53(2):352–4. doi:10.1373/clinchem.2006.076489.
80. Peaston RT, Lennard TW, Lai LC. Overnight excretion of urinary catecholamines and metabolites in the detection of pheochromocytoma. J Clin Endocrinol Metab. 1996;81:1378–84.
81. Neary NM, King KS, Pacak K. Drugs and pheochromocytoma—don't be fooled by every elevated metanephrine. N Engl J Med. 2011;364(23):2268–70. doi:10.1056/NEJMc1101502#SA1.
82. Jasperson KW, Kohlmann W, Gammon A, Slack H, Buchmann L, Hunt J, Kirchhoff AC, Baskin H, Shaaban A, Schiffman JD. Role of rapid sequence whole-body MRI screening in SDH-associated hereditary paraganglioma families. Familial Cancer. 2014;13(2):257–65. doi:10.1007/s10689-013-9639-6.
83. Maurea S, Cuocolo A, Reynolds JC, Neumann RD, Salvatore M. Diagnostic imaging in patients with paragangliomas. Computed tomography, magnetic resonance and MIBG scintigraphy comparison. Q J Nucl Med. 1996;40(4):365–71.
84. Kantorovich V, Pacak K. Pheochromocytoma and paraganglioma. Prog Brain Res. 2010;182:343–73. doi:10.1016/S0079-6123(10)82015-1.
85. Schmedtje JF Jr, Sax S, Pool JL, Goldfarb RA, Nelson EB. Localization of ectopic pheochromocytomas by magnetic resonance imaging. Am J Med. 1987;83(4):770–2.
86. Taieb D, Timmers HJ, Hindie E, Guillet BA, Neumann HP, Walz MK, Opocher G, et al. EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging. 2012;39(12):1977–95. doi:10.1007/s00259-012-2215-8.
87. Hoegerle S, Nitzsche E, Altehoefer C, Ghanem N, Manz T, Brink I, Reincke M, Moser E, Neumann HP. Pheochromocytomas: detection with 18F DOPA whole body PET—initial results. Radiology. 2002;222(2):507–12.
88. Pacak K, Eisenhofer G, Carrasquillo JA, Chen CC, Li ST, Goldstein DS. 6-[18F]fluorodopamine positron emission tomographic (PET) scanning for diagnostic localization of pheochromocytoma. Hypertension. 2001;38(1):6–8.
89. Pacak K, Eisenhofer G, Carrasquillo JA, Chen CC, Whatley M, Goldstein DS. Diagnostic localization of pheochromocytoma: the coming of age of positron emission tomography. Ann N Y Acad Sci. 2002;970:170–6.
90. Shapiro B, Gross MD, Shulkin B. Radioisotope diagnosis and therapy of malignant pheochromocytoma. Trends Endocrinol Metab. 2001;12(10):469–75.
91. Shulkin BL, Thompson NW, Shapiro B, Francis IR, Sisson JC. Pheochromocytomas: Imaging with 2-[Fluorine-18]fluoro-2-deoxy-D-glucose PET. Nucl Med. 1999;212:35–41.
92. Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Eisenhofer G, King KS, et al. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-Fluorodeoxyglucose (18F-FDG) positron emission tomography. J Natl Cancer Inst. 2012;104(9):700–8. doi:10.1093/jnci/djs188.
93. Timmers HJ, Taieb D, Pacak K. Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma. Horm Metab Res. 2012;44(5):367–72. doi:10.1055/s-0031-1299712.
94. Janssen I, Chen CC, Millo CM, Ling A, Taieb D, Lin FI, Adams KT, et al. PET/CT comparing (68)Ga-DOTATATE and other radiopharmaceuticals and in comparison with CT/MRI for the localization of sporadic metastatic pheochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging. 2016;43(10):1784–91. doi:10.1007/s00259-016-3357-x.
95. Janssen I, Chen CC, Taieb D, Patronas NJ, Millo CM, Adams KT, Nambuba J, et al. 68Ga-DOTATATE PET/CT in the localization of head and neck paragangliomas compared with other functional imaging modalities and CT/MRI. J Nucl Med. 2016;57(2):186–91. doi:10.2967/jnumed.115.161018.
96. Kroiss A, Putzer D, Uprimny C, Decristoforo C, Gabriel M, Santner W, Kranewitter C, et al. Functional imaging in phaeochromocytoma and neuroblastoma with 68Ga-DOTA-Tyr 3-octreotide positron emission tomography and 123I-metaiodobenzylguanidine. Eur J Nucl Med Mol Imaging. 2011;38(5):865–73. doi:10.1007/s00259-010-1720-x.

97. Maurice JB, Troke R, Win Z, Ramachandran R, Al-Nahhas A, Naji M, Dhillo W, et al. A comparison of the performance of (6)(8)Ga-DOTATATE PET/CT and (1)(2)(3)I-MIBG SPECT in the diagnosis and follow-up of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging. 2012;39(8):1266–70. doi:10.1007/s00259-012-2119-7.
98. Havekes B, King K, Lai EW, Romijn JA, Corssmit EP, Pacak K. New imaging approaches to phaeochromocytomas and paragangliomas. Clin Endocrinol. 2010;72(2):137–45. doi:10.1111/j.1365-2265.2009.03648.x.
99. Nakatani T, Hayama T, Uchida J, Nakamura K, Takemoto Y, Sugimura K. Diagnostic localization of extra-adrenal pheochromocytoma: comparison of (123)I-MIBG imaging and (131) I-MIBG imaging. Oncol Rep. 2002;9(6):1225–7.
100. Timmers HJ, Eisenhofer G, Carrasquillo JA, Chen CC, Whatley M, Ling A, Adams KT, Pacak K. Use of 6-[18F]-fluorodopamine positron emission tomography (PET) as first-line investigation for the diagnosis and localization of non-metastatic and metastatic phaeochromocytoma (PHEO). Clin Endocrinol. 2009;71(1):11–7. doi:10.1111/j.1365-2265.2008.03496.x.
101. Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, Adams KT, Solis D, Lenders JW, Pacak K. Superiority of fluorodeoxyglucose positron emission tomography to other functional imaging techniques in the evaluation of metastatic SDHB-associated pheochromocytoma and paraganglioma. J Clin Oncol. 2007;25(16):2262–9. doi:10.1200/JCO.2006.09.6297.
102. van der Harst E, de Herder WW, Bruining HA, Bonjer HJ, de Krijger RR, Lamberts SW, van de Meiracker AH, et al. [(123)I]metaiodobenzylguanidine and [(111)In]octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metab. 2001;86(2):685–93.
103. Van Der Horst-Schrivers AN, Jager PL, Boezen HM, Schouten JP, Kema IP, Links TP. Iodine-123 metaiodobenzylguanidine scintigraphy in localising phaeochromocytomas—experience and meta-analysis. Anticancer Res. 2006;26(2B):1599–604.
104. Bombardieri E, Giammarile F, Aktolun C, Baum RP, Bischof Delaloye A, Maffioli L, Moncayo R, et al. 131I/123I-metaiodobenzylguanidine (mIBG) scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging. 2010;37(12):2436–46. doi:10.1007/s00259-010-1545-7.
105. Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled metaiodobenzylguanidine (MIBG). Nucl Med Commun. 1992;13(7):513–21.
106. Stefanelli A, Treglia G, Bruno I, Rufini V, Giordano A. Pharmacological interference with 123I-metaiodobenzylguanidine: a limitation to developing cardiac innervation imaging in clinical practice? Eur Rev. Med Pharmacol Sci. 2013;17(10):1326–33.
107. Hartung-Knemeyer V, Rosenbaum-Krumme S, Buchbender C, Poppel T, Brandau W, Jentzen W, Antoch G, Forsting M, Bockisch A, Kuhl H. Malignant pheochromocytoma imaging with [124I]mIBG PET/MR. J Clin Endocrinol Metab. 2012;97(11):3833–4. doi:10.1210/jc.2012-1958.
108. Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Havekes B, Eisenhofer G, Martiniova L, Adams KT, Pacak K. Comparison of 18F-fluoro-L-DOPA, 18F-fluorodeoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2009;94(12):4757–67. doi:10.1210/jc.2009-1248.
109. Goldstein DS, Eisenhofer G, Dunn BB, Armando I, Lenders J, Grossman E, Holmes C, et al. Positron emission tomographic imaging of cardiac sympathetic innervation using 6-[18F] fluorodopamine: initial findings in humans. J Am Coll Cardiol. 1993;22(7):1961–71.
110. Shulkin BL, Wieland DM, Schwaiger MS, et al. PET scanning with hydroxyephedrine: A new approach to the localization of pheochromocytoma. J Nucl Med. 1992;33:1125–31.
111. Yamamoto S, Hellman P, Wassberg C, Sundin A. 11C-Hydroxyephedrine positron emission tomography imaging of pheochromocytoma: a single center experience over 11 years. J Clin Endocrinol Metab. 2012;97:2423–32. doi:10.1210/jc.2011-3342.
112. Chen CC, Carrasquillo JA. Molecular imaging of adrenal neoplasms. J Surg Oncol. 2012;106(5):532–42. doi:10.1002/jso.23162.

113. Timmers HJ, Hadi M, Carrasquillo JA, Chen CC, Martiniova L, Whatley M, Ling A, Eisenhofer G, Adams KT, Pacak K. The effects of carbidopa on uptake of 6-18F-Fluoro-L-DOPA in PET of pheochromocytoma and extraadrenal abdominal paraganglioma. J Nucl Med. 2007;48(10):1599–606. doi:10.2967/jnumed.107.042721.
114. Fiebrich HB, Brouwers AH, Kerstens MN, Pijl ME, Kema IP, de Jong JR, Jager PL, et al. 6-[F-18]Fluoro-L-dihydroxyphenylalanine positron emission tomography is superior to conventional imaging with (123)I-metaiodobenzylguanidine scintigraphy, computer tomography, and magnetic resonance imaging in localizing tumors causing catecholamine excess. J Clin Endocrinol Metab. 2009;94(10):3922–30. doi:10.1210/jc.2009-1054.
115. King KS, Chen CC, Alexopoulos DK, Whatley MA, Reynolds JC, Patronas N, Ling A, et al. Functional imaging of SDHx-related head and neck paragangliomas: comparison of 18F-fluorodihydroxyphenylalanine, 18F-fluorodopamine, 18F-fluoro-2-deoxy-D-glucose PET, 123I-metaiodobenzylguanidine scintigraphy, and 111In-pentetreotide scintigraphy. J Clin Endocrinol Metab. 2011;96(9):2779–85. doi:10.1210/jc.2011-0333.
116. Krenning EP, Kwekkeboom DJ, Pawels S, Kvols LK, Reubi JC. Somatostatin receptor scintigraphy. In: Freeman LM, editor. Nuclear Medicine Annual 1995. New York: Raven Press; 1995. p. 242–4.
117. Kaltsas G, Korbonits M, Heintz E, Mukherjee JJ, Jenkins PJ, Chew SL, Reznek R, et al. Comparison of somatostatin analog and meta-iodobenzylguanidine radionuclides in the diagnosis and localization of advanced neuroendocrine tumors. J Clin Endocrinol Metab. 2001;86(2):895–902.
118. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab. 2004;89(2):479–91. doi: 10.1210/jc.2003-031091.
119. Ambrosini V, Fanti S. 68Ga-DOTA-peptides in the diagnosis of NET. PET Clin. 2014;9(1):37–42. doi:10.1016/j.cpet.2013.08.007.
120. Fanti S, Ambrosini V, Tomassetti P, Castellucci P, Montini G, Allegri V, Grassetto G, Rubello D, Nanni C, Franchi R. Evaluation of unusual neuroendocrine tumours by means of 68Ga-DOTA-NOC PET. Biomed Pharmacother. 2008;62(10):667–71. doi:10.1016/j.biopha.2008.01.010.
121. Kroiss A, Putzer D, Decristoforo C, Uprimny C, Warwitz B, Nilica B, Gabriel M, et al. 68Ga-DOTA-TOC uptake in neuroendocrine tumour and healthy tissue: differentiation of physiological uptake and pathological processes in PET/CT. Eur J Nucl Med Mol Imaging. 2013;40(4):514–23. doi:10.1007/s00259-012-2309-3.
122. Kroiss A, Putzer D, Frech A, Decristoforo C, Uprimny C, Gasser RW, Shulkin BL, et al. A retrospective comparison between 68Ga-DOTA-TOC PET/CT and 18F-DOPA PET/CT in patients with extra-adrenal paraganglioma. Eur J Nucl Med Mol Imaging. 2013;40(12):1800–8. doi:10.1007/s00259-013-2548-y.
123. Naji M, Zhao C, Welsh SJ, Meades R, Win Z, Ferrarese A, Tan T, Rubello D, Al-Nahhas A. 68Ga-DOTA-TATE PET vs. 123I-MIBG in identifying malignant neural crest tumours. Mol Imaging Biol. 2011;13(4):769–75. doi:10.1007/s11307-010-0396-8.
124. Naswa N, Sharma P, Nazar AH, Agarwal KK, Kumar R, Ammini AC, Malhotra A, Bal C. Prospective evaluation of (6)(8)Ga-DOTA-NOC PET-CT in phaeochromocytoma and paraganglioma: preliminary results from a single centre study. Eur Radiol. 2012;22(3):710–9. doi:10.1007/s00330-011-2289-x.
125. Naswa N, Sharma P, Soundararajan R, Patnecha M, Lata S, Kumar R, Malhotra A, Bal C. Preoperative characterization of indeterminate large adrenal masses with dual tracer PET-CT using fluorine-18 fluorodeoxyglucose and gallium-68-DOTANOC: initial results. Diagn Interv Radiol. 2013;19(4):294–8. doi:10.5152/dir.2013.048.
126. Sharma P, Thakar A, Suman KCS, Dhull VS, Singh H, Naswa N, Reddy RM, et al. 68Ga-DOTANOC PET/CT for baseline evaluation of patients with head and neck paraganglioma. J Nucl Med. 2013;54(6):841–7. doi:10.2967/jnumed.112.115485.
127. Maher ER. Phaeochromocytoma and paraganglioma: next-generation sequencing and evolving Mendelian syndromes. Clin Med. 2014;14(4):440–4. doi:10.7861/clinmedicine.14-4-440.

128. Tsirlin A, Oo Y, Sharma R, Kansara A, Gliwa A, Banerji MA. Pheochromocytoma: a review. Maturitas. 2014;77(3):229–38. doi:10.1016/j.maturitas.2013.12.009.
129. Vicha A, Musil Z, Pacak K. Genetics of pheochromocytoma and paraganglioma syndromes: new advances and future treatment options. Curr Opin Endocrinol Diabetes Obes. 2013;20(3):186–91. doi:10.1097/MED.0b013e32835fcc45.
130. Amar L, Bertherat J, Baudin E, Ajzenberg C, Bressac-de Paillerets B, Chabre O, Chamontin B, et al. Genetic testing in pheochromocytoma or functional paraganglioma. J Clin Oncol. 2005;23(34):8812–8. doi: 10.1200/JCO.2005.03.1484.
131. Benn DE, Robinson BG. Genetic basis of phaeochromocytoma and paraganglioma. Best Pract Res Clin Endocrinol Metab. 2006;20(3):435–50. doi: 10.1016/j.beem.2006.07.005.
132. Mannelli M, Castellano M, Schiavi F, Filetti S, Giacche M, Mori L, Pignataro V, et al. Clinically guided genetic screening in a large cohort of italian patients with pheochromocytomas and/or functional or nonfunctional paragangliomas. J Clin Endocrinol Metab. 2009;94(5):1541–7. doi:10.1210/jc.2008-2419.
133. Eisenhofer G, Lenders JW, Timmers H, Mannelli M, Grebe SK, Hofbauer LC, Bornstein SR, et al. Measurements of plasma methoxytyramine, normetanephrine, and metanephrine as discriminators of different hereditary forms of pheochromocytoma. Clin Chem. 2011;57(3):411–20. doi:10.1373/clinchem.2010.153320.
134. Eisenhofer G, Pacak K, Huynh TT, Qin N, Bratslavsky G, Linehan WM, Mannelli M, et al. Catecholamine metabolomic and secretory phenotypes in phaeochromocytoma. Endocr Relat Cancer. 2011;18(1):97–111. doi:10.1677/ERC-10-0211.
135. Galan SR, Kann PH. Genetics and molecular pathogenesis of pheochromocytoma and paraganglioma. Clin Endocrinol. 2013;78(2):165–75. doi:10.1111/cen.12071.
136. Jafri M, Maher ER. The genetics of phaeochromocytoma: using clinical features to guide genetic testing. Eur J Endocrinol. 2012;166(2):151–8. doi:10.1530/EJE-11-0497.
137. Karasek D, Shah U, Frysak Z, Stratakis C, Pacak K. An update on the genetics of pheochromocytoma. J Hum Hypertens. 2013;27(3):141–7. doi:10.1038/jhh.2012.20.
138. Comino-Mendez I, Gracia-Aznarez FJ, Schiavi F, Landa I, Leandro-Garcia LJ, Leton R, Honrado E, et al. Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. Nat Genet. 2011;43(7):663–7. doi:10.1038/ng.861.
139. Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, Schipper J, et al. Germline mutations in nonsyndromic pheochromocytoma. N Engl J Med. 2002;346(19):1459–66.
140. Plouin PF, Fitzgerald P, Rich T, Ayala-Ramirez M, Perrier ND, Baudin E, Jimenez C. Metastatic pheochromocytoma and paraganglioma: focus on therapeutics. Horm Metab Res. 2012;44:390–9. doi:10.1055/s-0031-1299707.
141. Mazza A, Armigliato M, Marzola MC, Schiavon L, Montemurro D, Vescovo G, Zuin M, et al. Anti-hypertensive treatment in pheochromocytoma and paraganglioma: current management and therapeutic features. Endocrine. 2014;45(3):469–78. doi:10.1007/s12020-013-0007-y.
142. Chen H, Sippel RS, O'Dorisio MS, Vinik AI, Lloyd RV, Pacak K. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas. 2010;39(6):775–83. doi:10.1097/MPA.0b013e3181ebb4f0.
143. Kinney MA, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. J Cardiothorac Vasc Anesth. 2002;16(3):359–69.
144. Van Stratum M, Levarlet M, Lambilliotte JP, Lignian H, de Rood M. Use of labetalol during anesthesia for pheochromocytoma removal. Acta Anaesthesiol Belg. 1983;34(4):233–40.
145. Siddiqi HK, Yang HY, Laird AM, Fox AC, Doherty GM, Miller BS, Gauger PG. Utility of oral nicardipine and magnesium sulfate infusion during preparation and resection of pheochromocytomas. Surgery. 2012;152(6):1027–36. doi:10.1016/j.surg.2012.08.023.
146. Conzo G, Musella M, Corcione F, De Palma M, Avenia N, Milone M, Della Pietra C, et al. Laparoscopic treatment of pheochromocytomas smaller or larger than 6 cm. A clinical retrospective study on 44 patients. Laparoscopic adrenalectomy for pheochromocytoma. Ann Ital Chir. 2013;84(4):417–22.

147. Conzo G, Tartaglia E, Gambardella C, Esposito D, Sciascia V, Mauriello C, Nunziata A, et al. Minimally invasive approach for adrenal lesions: Systematic review of laparoscopic versus retroperitoneoscopic adrenalectomy and assessment of risk factors for complications. Int J Surg. 2016;28(Suppl 1):S118–23. doi:10.1016/j.ijsu.2015.12.042.
148. Wang W, Li P, Wang Y, Wang Y, Ma Z, Wang G, Gao J, Zhou H. Effectiveness and safety of laparoscopic adrenalectomy of large pheochromocytoma: a prospective, nonrandomized, controlled study. Am J Surg. 2015;210(2):230–5. doi:10.1016/j.amjsurg.2014.11.012.
149. Goers TA, Abdo M, Moley JF, Matthews BD, Quasebarth M, Brunt LM. Outcomes of resection of extra-adrenal pheochromocytomas/paragangliomas in the laparoscopic era: a comparison with adrenal pheochromocytoma. Surg Endosc. 2013;27(2):428–33. doi:10.1007/s00464-012-2451-9.
150. Kim HH, Kim GH, Sung GT. Laparoscopic adrenalectomy for pheochromocytoma: comparison with conventional open adrenalectomy. J Endourol. 2004;18(3):251–5. doi: 10.1089/089277904773582859.
151. Aliyev S, Karabulut K, Agcaoglu O, Wolf K, Mitchell J, Siperstein A, Berber E. Robotic versus laparoscopic adrenalectomy for pheochromocytoma. Ann Surg Oncol. 2013;20(13):4190–4. doi:10.1245/s10434-013-3134-z.
152. Arghami A, Dy BM, Bingener J, Osborn J, Richards ML. Single-port robotic-assisted adrenalectomy: feasibility, safety, and cost-effectiveness. JSLS. 2015;19(1):e2014 00218. doi:10.4293/JSLS.2014.00218.
153. Asher KP, Gupta GN, Boris RS, Pinto PA, Linehan WM, Bratslavsky G. Robot-assisted laparoscopic partial adrenalectomy for pheochromocytoma: the National Cancer Institute technique. Eur Urol. 2011;60(1):118–24. doi:10.1016/j.eururo.2011.03.046.
154. Benhammou JN, Boris RS, Pacak K, Pinto PA, Linehan WM, Bratslavsky G. Functional and oncologic outcomes of partial adrenalectomy for pheochromocytoma in patients with von Hippel-Lindau syndrome after at least 5 years of followup. J Urol. 2010;184(5):1855–9. doi:10.1016/j.juro.2010.06.102.
155. Kaye DR, Storey BB, Pacak K, Pinto PA, Linehan WM, Bratslavsky G. Partial adrenalectomy: underused first line therapy for small adrenal tumors. J Urol. 2010;184(1):18–25. doi:10.1016/j.juro.2010.03.052.
156. Sanford TH, Storey BB, Linehan WM, Rogers CA, Pinto PA, Bratslavsky G. Outcomes and timing for intervention of partial adrenalectomy in patients with a solitary adrenal remnant and history of bilateral phaeochromocytomas. BJU Int. 2011;107(4):571–5. doi:10.1111/j.1464-410X.2010.09568.x.
157. Alesina PF, Hinrichs J, Meier B, Schmid KW, Neumann HP, Walz MK. Minimally invasive cortical-sparing surgery for bilateral pheochromocytomas. Langenbeck's Arch Surg. 2012;397(2):233–8. doi:10.1007/s00423-011-0851-2.
158. Grubbs EG, Rich TA, Ng C, Bhosale PR, Jimenez C, Evans DB, Lee JE, Perrier ND. Long-term outcomes of surgical treatment for hereditary pheochromocytoma. J Am Coll Surg. 2013;216(2):280–9. doi:10.1016/j.jamcollsurg.2012.10.012.
159. Lee JE, Curley SA, Gagel RF, Evans DB, Hickey RC. Cortical-sparing adrenalectomy for patients with bilateral pheochromocytoma. Surgery. 1996;120:1064–70. discussion 1070
160. Neumann HP, Reincke M, Bender BU, Elsner R, Janetschek G. Preserved adrenocortical function after laparoscopic bilateral adrenal sparing surgery for hereditary pheochromocytoma. J Clin Endocrinol Metab. 1999;84(8):2608–10.
161. Neumann HP, Bender BU, Reincke M, Eggstein S, Laubenberger J, Kirste G. Adrenal-sparing surgery for phaeochromocytoma. Br J Surg. 1999;86(1):94–7.
162. Adjalle R, Plouin PF, Pacak K, Lehnert H. Treatment of malignant pheochromocytoma. Horm Metab Res. 2009;41(9):687–96. doi:10.1055/s-0029-1231025.
163. Arnas-Leon C, Sanchez V, Santana Suarez AD, Quintana Arroyo S, Acosta C, Martinez Martin FJ. Complete remission in metastatic pheochromocytoma treated with extensive surgery. Cureus. 2016;8(1):e447. doi:10.7759/cureus.447.
164. Ellis RJ, Patel D, Prodanov T, Sadowski S, Nilubol N, Adams K, Steinberg SM, Pacak K, Kebebew E. Response after surgical resection of metastatic pheochromocytoma and

paraganglioma: can postoperative biochemical remission be predicted? J Am Coll Surg. 2013;217(3):489–96. doi:10.1016/j.jamcollsurg.2013.04.027.
165. Buhl T, Mortensen J, Kjaer A. I-123 MIBG imaging and intraoperative localization of metastatic pheochromocytoma: a case report. Clin Nucl Med. 2002;27(3):183–5.
166. Una-Gorospe JA, Munoz-Iglesias J, De Sequera-Rahola M, Anton L. Usefulness of single photon emission computed tomography (SPECT)/computed tomography and radioguided surgery in a patient with recurrent pheochromocytoma. Indian J Nucl Med. 2013;28(1):59–60. doi:10.4103/0972-3919.116801.
167. Ramakrishna H. Pheochromocytoma resection: current concepts in anesthetic management. J Anaesthesiol Clin Pharmacol. 2015;31(3):317–23. doi:10.4103/0970-9185.161665.
168. Minami T, Adachi T, Fukuda K. An effective use of magnesium sulfate for intraoperative management of laparoscopic adrenalectomy for pheochromocytoma in a pediatric patient. Anesth Analg. 2002;95(5):1243–4.
169. Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Plouin PF. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. J Clin Endocrinol Metab. 2005;90(4):2110–6. doi: 10.1210/jc.2004-1398.
170. Plouin PF, Chatellier G, Fofol I, Corvol P. Tumor recurrence and hypertension persistence after successful pheochromocytoma operation. Hypertension. 1997;29(5):1133–9.
171. Linnoila RI, Keiser HR, Steinberg SM, Lack EE. Histopathology of benign versus malignant sympathoadrenal paragangliomas: clinicopathologic study of 120 cases including unusual histologic features. Hum Pathol. 1990;21(11):1168–80.
172. Eisenhofer G, Bornstein SR, Brouwers FM, Cheung NK, Dahia PL, de Krijger RR, Giordano TJ, et al. Malignant pheochromocytoma: current status and initiatives for future progress. Endocr Relat Cancer. 2004;11(3):423–36.
173. Eisenhofer G, Huynh TT, Hiroi M, Pacak K. Understanding catecholamine metabolism as a guide to the biochemical diagnosis of pheochromocytoma. Rev Endocr Metab Disord. 2001;2(3):297–311.
174. Stumvoll M, Fritsche A, Pickert A, Overkamp D. Features of malignancy in a benign pheochromocytoma. Horm Res. 1997;48(3):135–6.
175. Goldstein RE, O'Neill JA Jr, Holcomb GW 3rd, Morgan WM 3rd, Neblett WW 3rd, Oates JA, Brown N, et al. Clinical experience over 48 years with pheochromocytoma. Ann Surg. 1999;229(6):755–64.
176. Mundschenk J, Lehnert H. Malignant pheochromocytoma. Exp Clin Endocrinol Diabetes. 1998;106(5):373–6.
177. John H, Ziegler WH, Hauri D, Jaeger P. Pheochromocytomas: can malignant potential be predicted? Urology. 1999;53(4):679–83.
178. Angelousi A, Kassi E, Zografos G, Kaltsas G. Metastatic pheochromocytoma and paraganglioma. Eur J Clin Investig. 2015;45(9):986–97. doi:10.1111/eci.12495.
179. Baudin E, Habra MA, Deschamps F, Cote G, Dumont F, Cabanillas M, Arfi-Roufe J, et al. Therapy of endocrine disease: treatment of malignant pheochromocytoma and paraganglioma. Eur J Endocrinol. 2014;171(3):R111–22. doi:10.1530/EJE-14-0113.
180. Scholz T, Eisenhofer G, Pacak K, Dralle H, Lehnert H. Clinical review: Current treatment of malignant pheochromocytoma. J Clin Endocrinol Metab. 2007;92(4):1217–25. doi: 10.1210/jc.2006-1544.
181. Carrasquillo JA, Pandit-Taskar N, Chen CC. Radionuclide therapy of adrenal tumors. J Surg Oncol. 2012;106(5):632–42. doi:10.1002/jso.23196.
182. Carrasquillo JA, Pandit-Taskar N, Chen CC. I-131 metaiodobenzylguanidine therapy of pheochromocytoma and paraganglioma. Semin Nucl Med. 2016;46(3):203–14. doi:10.1053/j.semnuclmed.2016.01.011.
183. Loh KC, Fitzgerald PA, Matthay KK, Yeo PP, Price DC. The treatment of malignant pheochromocytoma with iodine-131 metaiodobenzylguanidine (131I-MIBG): a comprehensive review of 116 reported patients. J Endocrinol Investig. 1997;20(11):648–58.
184. Cecchin D, Schiavi F, Fanti S, Favero M, Manara R, Fassina A, Briani C, et al. Peptide receptor radionuclide therapy in a case of multiple spinal canal and cranial paragangliomas. J Clin Oncol. 2011;29(7):e171–4. doi:10.1200/JCO.2010.31.7131.

185. Garkavij M, Nickel M, Sjogreen-Gleisner K, Ljungberg M, Ohlsson T, Wingardh K, Strand SE, Tennvall J. 177Lu-[DOTA0,Tyr3] octreotate therapy in patients with disseminated neuroendocrine tumors: analysis of dosimetry with impact on future therapeutic strategy. Cancer. 2010;116(4 Suppl):1084–92. doi:10.1002/cncr.24796.
186. Gulenchyn KY, Yao X, Asa SL, Singh S, Law C. Radionuclide therapy in neuroendocrine tumours: a systematic review. Clin Oncol (R Coll Radiol). 2012;24(4):294–308. doi:10.1016/j.clon.2011.12.003.
187. Menda Y, O'Dorisio MS, Kao S, Khanna G, Michael S, Connolly M, Babich J, O'Dorisio T, Bushnell D, Madsen M. Phase I trial of 90Y-DOTATOC therapy in children and young adults with refractory solid tumors that express somatostatin receptors. J Nucl Med. 2010;51(10):1524–31. doi:10.2967/jnumed.110.075226.
188. Mundschenk J, Unger N, Schulz S, Hollt V, Steinke R, Lehnert H. Somatostatin receptor subtypes in human pheochromocytoma: subcellular expression pattern and functional relevance for octreotide scintigraphy. J Clin Endocrinol Metab. 2003;88(11):5150–7. doi: 10.1210/jc.2003-030262.
189. Plouin PF, Bertherat J, Chatellier G, Billaud E, Azizi M, Grouzmann E, Epelbaum J. Short-term effects of octreotide on blood pressure and plasma catecholamines and neuropeptide Y levels in patients with phaeochromocytoma: a placebo-controlled trial. Clin Endocrinol. 1995;42(3):289–94.
190. van Essen M, Krenning EP, Kooij PP, Bakker WH, Feelders RA, de Herder WW, Wolbers JG, Kwekkeboom DJ. Effects of therapy with [177Lu-DOTA0, Tyr3]octreotate in patients with paraganglioma, meningioma, small cell lung carcinoma, and melanoma. J Nucl Med. 2006;47(10):1599–606.
191. Zovato S, Kumanova A, Dematte S, Sansovini M, Bodei L, Di Sarra D, Casagranda E, et al. Peptide receptor radionuclide therapy (PRRT) with 177Lu-DOTATATE in individuals with neck or mediastinal paraganglioma (PGL). Horm Metab Res. 2012;44(5):411–4. doi:10.1055/s-0032-1311637.
192. Mamlouk MD, vanSonnenberg E, Stringfellow G, Smith D, Wendt A. Radiofrequency ablation and biopsy of metastatic pheochromocytoma: emphasizing safety issues and dangers. J Vasc Interv Radiol. 2009;20(5):670–3. doi:10.1016/j.jvir.2009.01.031.
193. McBride JF, Atwell TD, Charboneau WJ, Young WF Jr, Wass TC, Callstrom MR. Minimally invasive treatment of metastatic pheochromocytoma and paraganglioma: efficacy and safety of radiofrequency ablation and cryoablation therapy. J Vasc Interv Radiol. 2011;22(9):1263–70. doi:10.1016/j.jvir.2011.06.016.
194. Pacak K, Fojo T, Goldstein DS, Eisenhofer G, Walther MM, Linehan WM, Bachenheimer L, Abraham J, Wood BJ. Radiofrequency ablation: a novel approach for treatment of metastatic pheochromocytoma. J Natl Cancer Inst. 2001;93(8):648–9.
195. Venkatesan AM, Locklin J, Lai EW, Adams KT, Fojo AT, Pacak K, Wood BJ. Radiofrequency ablation of metastatic pheochromocytoma. J Vasc Interv Radiol. 2009;20(11):1483–90. doi:10.1016/j.jvir.2009.07.031.
196. Fishbein L. Pheochromocytoma and paraganglioma: genetics, diagnosis, and treatment. Hematol Oncol Clin North Am. 2016;30(1):135–50. doi:10.1016/j.hoc.2015.09.006.
197. Fishbein L, Bonner L, Torigian DA, Nathanson KL, Cohen DL, Pryma D, Cengel KA. External beam radiation therapy (EBRT) for patients with malignant pheochromocytoma and non-head and -neck paraganglioma: combination with 131I-MIBG. Horm Metab Res. 2012;44(5):405–10. doi:10.1055/s-0032-1308992.
198. Vogel J, Atanacio AS, Prodanov T, Turkbey BI, Adams K, Martucci V, Camphausen K, Fojo AT, Pacak K, Kaushal A. External beam radiation therapy in treatment of malignant pheochromocytoma and paraganglioma. Front Oncol. 2014;4:166. doi:10.3389/fonc.2014.00166.
199. Jackson CG. Glomus tympanicum and glomus jugulare tumors. Otolaryngol Clin N Am. 2001;34(5):941–70. vii
200. Chino JP, Sampson JH, Tucci DL, Brizel DM, Kirkpatrick JP. Paraganglioma of the head and neck: long-term local control with radiotherapy. Am J Clin Oncol. 2009;32(3):304–7. doi:10.1097/COC.0b013e318187dd94.

201. Guss ZD, Batra S, Limb CJ, Li G, Sughrue ME, Redmond K, Rigamonti D, et al. Radiosurgery of glomus jugulare tumors: a meta-analysis. Int J Radiat Oncol Biol Phys. 2011;81(4):e497–502. doi:10.1016/j.ijrobp.2011.05.006.
202. Hafez RF, Morgan MS, Fahmy OM. An intermediate term benefits and complications of gamma knife surgery in management of glomus jugulare tumor. World J Surg Oncol. 2016;14(1):36. doi:10.1186/s12957-016-0779-7.
203. Schuster D, Sweeney AD, Stavas MJ, Tawfik KY, Attia A, Cmelak AJ, Wanna GB. Initial radiographic tumor control is similar following single or multi-fractionated stereotactic radiosurgery for jugular paragangliomas. Am J Otolaryngol. 2016;37(3):255–8. doi:10.1016/j.amjoto.2016.01.002.
204. Averbuch SD, Steakley CS, Young RC, Gelmann EP, Goldstein DS, Stull R, Keiser HR. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Ann Intern Med. 1988;109(4):267–73.
205. Ayala-Ramirez M, Feng L, Habra MA, Rich T, Dickson PV, Perrier N, Phan A, Waguespack S, Patel S, Jimenez C. Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas: insights from the largest single-institutional experience. Cancer. 2012;118(11):2804–12. doi:10.1002/cncr.26577.
206. Huang H, Abraham J, Hung E, Averbuch S, Merino M, Steinberg SM, Pacak K, Fojo T. Treatment of malignant pheochromocytoma/paraganglioma with cyclophosphamide, vincristine, and dacarbazine: recommendation from a 22-year follow-up of 18 patients. Cancer. 2008;113(8):2020–8. doi: 10.1002/cncr.23812.
207. Nomura K, Kimura H, Shimizu S, Kodama H, Okamoto T, Obara T, Takano K. Survival of patients with metastatic malignant pheochromocytoma and efficacy of combined cyclophosphamide, vincristine, and dacarbazine chemotherapy. J Clin Endocrinol Metab. 2009;94(8):2850–6. doi: 10.1210/jc.2008-2697.
208. Tanabe A, Naruse M, Nomura K, Tsuiki M, Tsumagari A, Ichihara A. Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine in patients with malignant pheochromocytoma and paraganglioma. Horm Cancer. 2013;4(2):103–10. doi:10.1007/s12672-013-0133-2.
209. He J, Makey D, Fojo T, Adams KT, Havekes B, Eisenhofer G, Sullivan P, Lai EW, Pacak K. Successful chemotherapy of hepatic metastases in a case of succinate dehydrogenase subunit B-related paraganglioma. Endocrine. 2009;36(2):189–93. doi: 10.1007/s12020-009-9219-6.
210. Bravo EL, Kalmadi SR, Gill I. Clinical utility of temozolomide in the treatment of malignant paraganglioma: a preliminary report. Horm Metab Res. 2009;41(9):703–6. doi:10.1055/s-0029-1224135.
211. Kruijtzer CM, Beijnen JH, Swart M, Schellens JH. Successful treatment with paclitaxel of a patient with metastatic extra- adrenal pheochromocytoma (paraganglioma). A case report and review of the literature. Cancer Chemother Pharmacol. 2000;45(5):428–31. doi: 10.1007/s002800051013.
212. Kulke MH, Stuart K, Enzinger PC, Ryan DP, Clark JW, Muzikansky A, Vincitore M, Michelini A, Fuchs CS. Phase II study of temozolomide and thalidomide in patients with metastatic neuroendocrine tumors. J Clin Oncol. 2006;24(3):401–6. doi:10.1200/JCO.2005.03.6046.
213. Mora J, Cruz O, Parareda A, Sola T, de Torres C. Treatment of disseminated paraganglioma with gemcitabine and docetaxel. Pediatr Blood Cancer. 2009;53(4):663–5. doi:10.1002/pbc.22006.
214. Jochmanova I, Yang C, Zhuang Z, Pacak K. Hypoxia-inducible factor signaling in pheochromocytoma: turning the rudder in the right direction. J Natl Cancer Inst. 2013;105(17):1270–83. doi:10.1093/jnci/djt201.
215. Jochmanova I, Zhuang Z, Pacak K. Pheochromocytoma: gasping for air. Horm Cancer. 2015;6(5–6):191–205. doi:10.1007/s12672-015-0231-4.
216. Favier J, Amar L, Gimenez-Roqueplo AP. Paraganglioma and phaeochromocytoma: from genetics to personalized medicine. Nat Rev. Endocrinol. 2015;11(2):101–11. doi:10.1038/nrendo.2014.188.

217. Justus CR, Sanderlin EJ, Yang LV. Molecular connections between cancer cell metabolism and the tumor microenvironment. Int J Mol Sci. 2015;16(5):11055–86. doi:10.3390/ijms160511055.
218. Wigerup C, Pahlman S, Bexell D. Review: therapeutic targeting of hypoxia and hypoxia-inducible factors in cancer. Pharmacol Ther. 2016;164:152–69. doi:10.1016/j.pharmthera.2016.04.009.
219. Granja S, Pinheiro C, Reis RM, Martinho O, Baltazar F. Glucose addiction in cancer therapy: advances and drawbacks. Curr Drug Metab. 2015;16(3):221–42. doi: 10.2174/1389200216666150602145145.
220. Jin L, Alesi GN, Kang S. Glutaminolysis as a target for cancer therapy. Oncogene. 2015;35:3619–25. doi:10.1038/onc.2015.447.
221. Kroemer G, Pouyssegur J. Tumor cell metabolism: cancer's Achilles' heel. Cancer Cell. 2008;13(6):472–82. doi:10.1016/j.ccr.2008.05.005.
222. Mashima T, Seimiya H, Tsuruo T. De novo fatty-acid synthesis and related pathways as molecular targets for cancer therapy. Br J Cancer. 2009;100(9):1369–72. doi:10.1038/sj.bjc.6605007.
223. Mullen GE, Yet L. Progress in the development of fatty acid synthase inhibitors as anticancer targets. Bioorg Med Chem Lett. 2015;25(20):4363–9. doi:10.1016/j.bmcl.2015.08.087.
224. Vander Heiden MG. Targeting cancer metabolism: a therapeutic window opens. Nat Rev. Drug Discov. 2011;10(9):671–84. doi:10.1038/nrd3504.
225. Iacobazzi V, Infantino V. Citrate—new functions for an old metabolite. Biol Chem. 2014;395(4):387–99. doi:10.1515/hsz-2013-0271.
226. Jochmanova I, Pacak K. Pheochromoctyoma: the first metabolic endocrine cancer. Clin Cancer Res. 2016;22:5001–11. doi: 10.1158/1078-0432.CCR-16-0606.
227. Aita Y, Ishii KA, Saito Y, Ikeda T, Kawakami Y, Shimano H, Hara H, Takekoshi K. Sunitinib inhibits catecholamine synthesis and secretion in pheochromocytoma tumor cells by blocking VEGF receptor 2 via PLC-gamma-related pathways. Am J Physiol Endocrinol Metab. 2012;303(8):E1006–14. doi:10.1152/ajpendo.00156.2012.
228. Saito Y, Tanaka Y, Aita Y, Ishii KA, Ikeda T, Isobe K, Kawakami Y, Shimano H, Hara H, Takekoshi K. Sunitinib induces apoptosis in pheochromocytoma tumor cells by inhibiting VEGFR2/Akt/mTOR/S6 K1 pathways through modulation of Bcl-2 and BAD. Am J Physiol Endocrinol Metab. 2012;302(6):E615–25. doi:10.1152/ajpendo.00035.2011.
229. Ayala-Ramirez M, Chougnet CN, Habra MA, Palmer JL, Leboulleux S, Cabanillas ME, Caramella C, et al. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. J Clin Endocrinol Metab. 2012;97(11):4040–50. doi:10.1210/jc.2012-2356.
230. Jimenez C, Cabanillas ME, Santarpia L, Jonasch E, Kyle KL, Lano EA, Matin SF, et al. Use of the tyrosine kinase inhibitor sunitinib in a patient with von Hippel-Lindau disease: targeting angiogenic factors in pheochromocytoma and other von Hippel-Lindau disease-related tumors. J Clin Endocrinol Metab. 2009;94(2):386–91.
231. Joshua AM, Ezzat S, Asa SL, Evans A, Broom R, Freeman M, Knox JJ. Rationale and evidence for sunitinib in the treatment of malignant paraganglioma/pheochromocytoma. J Clin Endocrinol Metab. 2009;94(1):5–9. doi:10.1210/jc.2008-1836.
232. Prochilo T, Savelli G, Bertocchi P, Abeni C, Rota L, Rizzi A, Zaniboni A. Targeting VEGF-VEGFR pathway by sunitinib in peripheral primitive neuroectodermal tumor, paraganglioma and epithelioid hemangioendothelioma: three case reports. Case Rep Oncol. 2013;6(1):90–7. doi:10.1159/000348429.
233. Druce MR, Kaltsas GA, Fraenkel M, Gross DJ, Grossman AB. Novel and evolving therapies in the treatment of malignant phaeochromocytoma: experience with the mTOR inhibitor everolimus (RAD001). Horm Metab Res. 2009;41(9):697–702. doi:10.1055/s-0029-1220687.
234. Oh DY, Kim TW, Park YS, Shin SJ, Shin SH, Song EK, Lee HJ, Lee KW, Bang YJ. Phase 2 study of everolimus monotherapy in patients with nonfunctioning neuroendocrine tumors or pheochromocytomas/paragangliomas. Cancer. 2012;118(24):6162–70. doi:10.1002/cncr.27675.

235. Cao S, Cao R, Liu X, Luo X, Zhong W. Design, synthesis and biological evaluation of novel benzothiazole derivatives as selective PI3Kbeta inhibitors. Molecules. 2016;21(7):876. doi:10.3390/molecules21070876.
236. Wong MH, Xue A, Baxter RC, Pavlakis N, Smith RC. Upstream and downstream co-inhibition of mitogen-activated protein kinase and PI3K/Akt/mTOR pathways in pancreatic ductal adenocarcinoma. Neoplasia. 2016;18(7):425–35. doi:10.1016/j.neo.2016.06.001.
237. Peloton Therapeutics, Inc. A Phase 1, dose-escalation trial of PT2385 tablets in patients with advanced clear cell renal cell Carcinoma; 2014. https://clinicaltrials.gov/ct2/show/NCT02293980. Accessed 11 May 2016.
238. Cervantes-Madrid D, Romero Y, Duenas-Gonzalez A. Reviving lonidamine and 6-Diazo-5-oxo-L-norleucine to be used in combination for metabolic cancer therapy. Biomed Res Int. 2015;2015:690492. doi:10.1155/2015/690492.
239. Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene. 2006;25(34):4633–46. doi:10.1038/sj.onc.1209597.
240. Yang C, Matro JC, Huntoon KM, Ye DY, Huynh TT, Fliedner SM, Breza J, Zhuang Z, Pacak K. Missense mutations in the human SDHB gene increase protein degradation without altering intrinsic enzymatic function. FASEB J. 2012;26(11):4506–16. doi:10.1096/fj.12-210146.
241. Letouze E, Martinelli C, Loriot C, Burnichon N, Abermil N, Ottolenghi C, Janin M, et al. SDH mutations establish a hypermethylator phenotype in paraganglioma. Cancer Cell. 2013;23(6):739–52. doi:10.1016/j.ccr.2013.04.018.