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Genetics, diagnosis, management and future directions of research of pheochromocytoma and paraganglioma: a position statement and consensus of the Working Group on endocrine hypertension of the European society of hypertension

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Pheochromocytoma and paraganglioma (PPGL) are chromaffin cell tumours that require timely diagnosis because of their potentially serious cardiovascular and sometimes life-threatening sequelae. Tremendous progress in biochemical testing, imaging, genetics and pathophysiological understanding of the tumours has far-reaching implications for physicians dealing with hypertension and more importantly affected patients. Because hypertension is a classical clinical clue for PPGL, physicians involved in hypertension care are those who are often the first to consider this diagnosis. However, there have been profound changes in how PPGLs are discovered; this is often now based on incidental findings of adrenal or other masses during imaging and increasingly during surveillance based on rapidly emerging new hereditary causes of PPGL. We therefore address the relevant genetic causes of PPGLs and outline how genetic testing can be incorporated within clinical care. In addition to conventional imaging (computed tomography, MRI), new functional imaging approaches are evaluated. The novel knowledge of genotype-phenotype relationships, linking distinct genetic causes of disease to clinical behaviour and biochemical phenotype, provides the rationale for patient-tailored strategies for diagnosis, follow-up and surveillance. Most appropriate preoperative evaluation and preparation of patients are reviewed, as is minimally invasive surgery. Finally, we discuss risk factors for developing metastatic disease and how they may facilitate personalised follow-up. Experts from the European Society of Hypertension have prepared this position document that summarizes the current knowledge in epidemiology, genetics, diagnosis, treatment and surveillance of PPGL.

Keywords: catecholamines, imaging, metanephrines, paraganglioma, pheochromocytoma

Abbreviations: 123I-MIBG, 123I-metaiodobenzylguanidine; 18F-FDOPA, 18F-

fluorodihydroxy-phenylalanine; ATRX, alpha-thalassemia/mental retardation syndrome X-linked; BP, blood pressure; CSDE1, cold-shock domain containing E1; CT, computed tomography; HIF2 α , hypoxia inducible factor 2 α ; HNPGL, head/neck paraganglioma; LC-ECD, liquid chromatography with electrochemical detection; LC-MS/MS, liquid

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chromatography with tandem mass spectrometry; MAML3, MAMsterMind-Like 3; MAX MYC, associated factor X; MDH2, malate dehydrogenase 2; MEN2, multiple endocrine neoplasia type 2; MRI, magnetic resonance imaging; NF1, neurofibromatosis type 1; NGS, next-generation sequencing; PET, positron emission tomography; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma; RET, rearranged during transfection; SDHA, succinate dehydrogenase subunit A; SDHAF2, succinate dehydrogenase complex assembly factor 2; SDHB, succinate dehydrogenase subunit B; SDHC, succinate dehydrogenase subunit C; SDHD, succinate dehydrogenase subunit D; SLC25A11, solute carrier family 25 member 11; TCGA, the cancer genome atlas; TERT, telomerase reverse transcriptase; TMEM127, transmembrane domain protein 127; VHL, von Hippel-Lindau; VUS, variants of unknown significance

Consensus point

(1) Increased incidence of PPGLs likely reflects the changing mode of discovery of these tumours; the spectrum of indications for biochemical testing now includes not only signs and symptoms but also an incidentally detected adrenal mass and genetic causes or syndromes for which periodic surveillance is mandatory.

CLINICAL PRESENTATION AND INDICATIONS FOR PHAEOCHROMOCYTOMAS AND SYMPATHETIC PARAGANGLIOMA SCREENING

The heterogeneous clinical presentation of PPGLs is well established, but this is near exclusively based on retrospective series with most studies involving no comparisons to patients in whom PPGLs were suspected and excluded [14–16]. In a recent prospective multicentric series of 245 patients with PPGLs, reasons for disease discovery included signs and symptoms in 37% of patients, incidentalomas in 36% and surveillance in 27% of patients [17]. Prevalences of PPGLs for the latter situations are much higher than among patients tested due to signs and symptoms of presumed catecholamine excess. Among adrenal incidentaloma, about 7% represent pheochromocytoma [18], whereas among unselected patients tested for PPGLs, prevalences are less than 1% [19], indicating even lower prevalences among those tested due to signs and symptoms. Thus, the clinical presentation of the patient in terms of prevalence or likelihood for PPGL is a key first consideration for personalised approaches for diagnosis and management.

Signs and symptoms

The diverse and variable signs and symptoms of PPGL are related to the amounts, proportions and continuous or episodic secretory nature of catecholamines released by the tumours. Paroxysmal symptoms are a characteristic feature, presumably due to episodic secretory activity. Such symptoms may occur spontaneously or may be provoked by triggers, including exercise, abdominal pressure, large meals, medications (Supplemental Table 1, <http://links.lww.com/HJH/B310>), stress, alcohol and food (e.g. tyramine in some cheeses) [12,14,20–22].

In the above and other circumstances, PPGLs can present with life-threatening cardiovascular manifestations, including hypertensive crisis, myocardial infarction, brady and tachyarrhythmias, Takotsubo cardiomyopathy and acute heart failure. Rarely, patients with a PPGL present with low blood pressure or even with circulatory shock that may occasionally precede a multisystem crisis [23,24].

Recent studies have shown that the classic signs and symptoms occur more rarely than previously assumed. A recent meta-analysis showed that headache, palpitations and sweating occurred in 60, 59 and 52% of patients, whereas other symptoms occurred at a much lower frequency [25]. A further prospective study found that no single symptom occurred in more than 65% of patients with PPGL, including those tested because of signs and symptoms of presumed catecholamine excess. Moreover,

INTRODUCTION

Pheochromocytomas and sympathetic paragangliomas (PPGLs) are rare neuroendocrine tumours. Eighty to eighty-five percent are pheochromocytomas arising from the adrenal medulla. Fifteen to twenty percent are sympathetic paragangliomas arising from the sympathetic ganglia in thorax, abdomen and pelvis [1]. In the head and neck region, paragangliomas have a parasympathetic origin (HNPPGLs) [2].

Among the few epidemiological studies on PPGLs, most are from the previous century. Prevalences in autopsy studies amount to 0.05%, indicating that the diagnosis of PPGL is missed during life in substantial numbers of patients [3,4]. In addition, the reported median delay in the diagnosis is about 3 years [5]. PPGLs are considered as a ‘white raven’ with quoted prevalences varying from 0.2 to 0.6% in hypertensive patients to less than 0.05% in the general population. The annual incidence of PPGLs is about 5 cases per million per year. The most recent nationwide study performed in the Netherlands demonstrated an age-standardized incidence rate of 0.46 [95% confidence interval (95% CI): 0.39–0.53] and 0.11 (95% CI: 0.09–0.13) per 100 000 person-years for pheochromocytoma and sympathetic paraganglioma, respectively [6]. These incidences are higher than reported in earlier studies [7,8]; in line with this the Dutch study noted a near doubling of the incidence from 1995 to 2015, likely reflecting higher rates of detection in part due to increased use and improvement of imaging modalities [6,9]. Indeed, two recent retrospective series of patients with PPGLs reported that nearly two-thirds were discovered as incidentalomas [10,11]. Increasing numbers of individuals and family members in whom germline mutations for one of the known PPGL susceptibility genes have been detected are now also being routinely screened for PPGL, thus also impacting detected incidence [12,13].

The working group on Endocrine Hypertension of the European Society of Hypertension prepared this consensus document to review the available knowledge on genetics, diagnosis, treatment and surveillance of PPGL. We also provide a perspective on the next challenges and future directions of research on this field.

TABLE 1. Signs and symptoms in patients with and without PPGL enrolled in the full study cohort (N = 2017) and three different patient subpopulations according to their clinical presentation^a

	All patients		Signs and symptoms		Incidentaloma		Surveillance	
	PPGL	No PPGL	PPGL	No PPGL	PPGL	No PPGL	PPGL	No PPGL
N	243	1774	89	1170	88	387	66	217
BMI (kg/m ²)	25 ^b	28	25 ^b	28	25 ^b	29	25 ^b	27
Heart rate (b/min)	79 ^b	72	81 ^b	72	78 ^b	73	77 ^b	70
Pallor (%)	26 ^b	13	37 ^b	15	21 ^b	10	18 ^b	7
Sweating (%)	46 ^b	28	55 ^b	30	47 ^b	25	32 ^b	21
Palpitations (%)	46 ^b	36	65 ^b	44	46 ^b	22	21	19
Tremor (%)	25 ^b	15	33 ^b	18	21 ^b	8	18 ^b	6
Nausea /vomiting (%)	21 ^b	11	26 ^b	12	18	11	20 ^b	10
Symptom score $\geq 3^c$	42	18	56	21	40	13	28	1
Hypertension (%)	83	85	95	93	80	78	71	58
Headaches (%)	38	39	46	45	39	29	27	25
Weakness (%)	42 ^b	35	51 ^b	36	34	32	42	32
Panic/anxiety (%)	25	25	37	32	19	14	15 ^b	7
Flushing (%)	20	23	21	27	23	17	14	14
Constipation (%)	14 ^b	9	17 ^b	9	10	9	14	7

A cut-off value of symptom score of 3 is used to indicate an increased (≥ 3) or decreased (< 3) likelihood of PPGL.

PPGL, pheochromocytoma or paraganglioma.

^aThe full study cohort of the Prospective Monoamine-Producing Tumor (PMT) study (modified from [17]).

^bSignificant differences between patients with and without PPGL.

^cSymptom score: one point for each sign: BMI < 25 kg/m², heart rate ≥ 85 beats/min, pallor, sweating, palpitations, tremor and nausea; a negative point for obesity.

for several symptoms, there were little or no differences between patients in whom tumours were confirmed versus excluded (Table 1) [17].

Hypertension, even paroxysmal is also not a specific sign of PPGL [25]. However, ambulatory blood pressure in PPGL patients may show large BP variation and a decreased nocturnal BP fall, or even a nondipping BP pattern and BP elevation during the night [26–28]. Indiscriminate testing for PPGL in patients with uncomplicated hypertension is not indicated due to lack of cost-effectiveness.

Patients with PPGL are characterized not only by a higher frequency of palpitations but also by a higher heart rate as compared with patients without PPGL [17,25]. Diabetes and prediabetes are other signs of the hyperadrenergic state. In young hypertensive patients (≤ 50 years) who are not overweight (BMI < 25 kg/m²), the presence of diabetes is a useful clinical clue to search for a PPGL [29]. Moreover, PPGL patients are more often characterized by lower BMI than those without PPGL [12,14,20,30]. However, obesity does not exclude a PPGL. Clinical features that differ between patients in whom PPGLs have been confirmed versus excluded include lower BMI, increased heart rate, pallor, sweating, palpitations, tremor and nausea (actively asked to patients) [17]. Using a score system for these features as outlined in Table 1 enables further personalized approaches for diagnosis and management based on refining estimates of disease risk according to prevalence.

Head and neck paragangliomas

Head and neck paragangliomas (HNPGs) can be sporadic or can occur as part of hereditary syndromes in up to 40% with variable penetrance and increased risk for tumour multiplicity. Most HNPGs do not produce significant amounts of catecholamines so that presence of signs of

symptoms of catecholamine excess rarely represents a mode for their discovery. They are more often discovered during imaging studies or revealed by the presence of a temporal bone or cervical mass with in advanced stages causing compression or infiltration of adjacent structures, thus leading to hearing loss, pulsatile tinnitus, dysphagia and cranial nerve palsies [31].

Adrenal incidentaloma

All patients with adrenal incidentaloma with tumour density more than 10 HU should be screened for PPGL even in the absence of hypertension [18,32–35]. This is also justified by the finding that hypertension among patients with adrenal incidentalomas is not more frequent in patients with PPGL than in those without PPGL [17]. It should be emphasized that a diagnosis of PPGL should be also considered in the differential diagnosis of incidentally discovered retroperitoneal masses, especially when some features of catecholamine excess are present.

Surveillance screening

Routine screening for PPGL is recommended in patients with known mutations predisposing for PPGL, syndromic features suggesting hereditary PPGL and a previous history of PPGL. In these patients, signs and symptoms of PPGL are less often expressed mostly due to the small size of their tumours detected earlier than in other cases [17,36].

Screening for pheochromocytomas and sympathetic paragangliomas is recommended in patients with

- (1) Signs and symptoms of PPGL: spontaneous or provoked;
- (2) Cardiovascular events with signs/symptoms indicative for PPGL;

- (3) Adrenal incidentaloma (with or without hypertension) if density is more than 10 HU;
- (4) Young (≤ 50 years), lean individuals ($\text{BMI} < 25 \text{ kg/m}^2$) with diabetes type 2 with or without signs/symptoms of catecholamine excess;
- (5) Carrier of a germline mutation in one of the PPGL susceptibility genes;
- (6) Syndromic features suggesting genetically determined or syndromic PPGL;
- (7) Previous history or family history of PPGL.

Consensus points

- (2) Prevalence of PPGL in patients presenting with adrenal incidentaloma, mutations of tumour susceptibility genes, specific syndromic features and family or past history of a PPGL is relatively high compared to patients presenting with signs and symptoms alone
- (3) Likelihood of a PPGL can be assessed from the combination of prevalence (e.g. low in patients with clinical signs and symptoms, high in patients with adrenal incidentaloma) and presence of clinical features (e.g. palpitations)
- (4) Sustained hypertension cannot be considered as a highly specific sign of a PPGL, as it is also very prevalent in patients without PPGL.

BIOCHEMICAL DIAGNOSIS OF PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

Over the past two decades, improved understanding of catecholamine metabolism has led to a shift in emphasis from catecholamines to plasma or urinary metanephrines for biochemical diagnosis. Improved analytical accuracy attained using liquid chromatography with electrochemical detection (LC-ECD) or tandem mass spectrometry (LC-MS/MS) have also been instrumental to improved biochemical diagnosis of PPGL [37,38]. Biochemical proof of a PPGL is a prerequisite for the next diagnostic step of imaging, except for seriously ill patients in the ICU in whom biochemical testing is insufficiently reliable. These patients should go directly to imaging [12,39]. This also applies to patients in whom a PPGL is suspected but who are known not to produce catecholamines.

Consensus point

- (5) In nonemergency situations, biochemical testing should precede imaging whenever a PPGL is suspected.

What is the preferred initial biochemical test?

For first-line screening, measurements of plasma or urinary-free normetanephrine and metanephrine are the most accurate tests to detect or exclude a PPGL [12,40]. Inclusion of 3-methoxytyramine is useful for detecting dopamine-producing PPGLs when measured in plasma but not urine. Both plasma and urinary free metabolites have near maximal negative predictive values ($>99\%$) at similar specificities (94%) [40–42]. Measurements in plasma show similar diagnostic accuracy as those in urine in patients at low risk, such as those tested due to signs and symptoms, but are superior to those in urine in patients at high risk for a PPGL, such as those tested due to an incidentaloma or as part of surveillance screening [40]. Currently, most routine laboratories

still measure deconjugated metanephrines (free and conjugated metanephrines) in 24-h urine. This causes more false-positive test results than with free metanephrines, supporting a shift to measurements of free metanephrines.

LC-MS/MS is currently the preferred assay method because of its optimal analytical accuracy, cost-effectiveness and minimal analytical interference from drugs [38,41]. If local normative data are lacking, published reference intervals may be applied [43]. Of note, immunoassays often underestimate plasma metanephrines, negatively impacting diagnostic performance [44]. An activated sympathetic nervous system during biochemical testing is associated with high rates of false-positive results and compromised diagnostic accuracy [45–47]. Sampling blood for plasma measurements in particular should therefore be carried out under stress-free conditions in the supine position (Supplemental file §1, <http://links.lww.com/HJH/B310>).

Consensus points

- (6) Measurements of plasma or urinary-free metanephrines are the most accurate tests to detect or exclude a PPGL.
- (7) LC-MS/MS is currently the preferred assay method because of its optimal analytical accuracy, cost-effectiveness and minimal analytical interference from drugs.
- (8) To circumvent false-positive test results, testing for plasma-free metanephrines requires blood sampling after at least 20 min of supine rest. If not possible, urinary measurements of free metanephrines provide an alternative.

Personalized interpretation of test results

In addition to strict compliance of blood sampling after supine rest, correct and reliable interpretation of test results can only be achieved using appropriate reference intervals, also established after supine rest [12,40]. Use of personalised age-specific reference intervals for plasma normetanephrine and sex-specific reference intervals for urinary metanephrines optimizes diagnostic performance [43]. In patients with chronic kidney disease, higher specific upper cut-off values should be applied [48].

The nearly maximal negative predictive value of both plasma and urine tests implies that negative test results virtually exclude a PPGL. Exceptions include patients with tumours that are either small or those such as some HNPGLs that do not synthesize catecholamines; most of these do not cause signs and symptoms of catecholamine excess.

Consensus point

- (10) Plasma or urinary metanephrines in the normal range reliably exclude a PPGL in symptomatic patients.

In patients tested because of hereditary risk, choice of test and interpretation of test results should take into account the nature of the impacted gene. In patients with PPGLs due to mutations of *RET*, *NF1* and related genes involved in kinase signalling the focus should be on both metanephrine and normetanephrine, as almost always the first and invariably both metabolites are elevated [49]. In contrast, for mutations of genes that result of stabilization of hypoxia-inducible factors and epigenetic silencing of phenylethanolamine N-methyltransferase, the enzyme that converts noradrenaline into adrenaline (e.g. mutations of

TABLE 2. Medications that may cause falsely elevated results for plasma and urinary metanephrines due to pharmacodynamic interference

	Plasma and urine		
	Normetanephrine	Metanephrine	3-Methoxytyramine
Antidepressants	++	–	–
Phenoxylbenzamine	++	–	–
MAO-inhibitors	++	++	–
Sympathomimetics	+	+	–
Levodopa	–	–	+++

++ clear increase; + mild increase; –no increase.
MAO, monoamine oxidase.

VHL and *SDHx* genes) the focus should be on normetanephrine, as these tumours do not produce adrenaline. For patients with *SDHx* mutations or in whom there is the possibility of metastatic disease, plasma measurements should include 3-methoxytyramine.

Interpretations of a positive test result should also take into account pretest prevalence (e.g. 7% in a patient with incidentaloma) and features about the patient that can be further used to assess likely risk of disease [17]. Such considerations can then be used to assess posttest probability of a tumour based on both the extent of increase of a specific metabolite above the cut-offs and whether that increase is also accompanied by an increase in another metabolite [40]. Increments in any plasma metabolite in excess of two-fold above the upper cutoff or increases in two or more metabolites are very rare in patients without PPGLs, but occur in over 80% of patients with PPGL. In such patients, the likelihood of a PPGL is sufficiently high to justify imaging studies regardless of pretest prevalence. In other patients with smaller increases of single metabolites, posttest probability must consider pretest risk. In such cases, the clonidine suppression test can be helpful to differentiate false-positive from true-positive test results [45,50].

Falsely elevated test results [46,47] can occur in patients with any clinical condition associated with chronically elevated sympathetic activity such as heart failure or obstructive sleep apnoea syndrome. Inappropriate sampling conditions, drug interferences (Table 2) and incorrectly applied reference intervals are other situations that can lead to false-positive results. Interpretation of test results in such patients requires care, as elevations can reach levels that would otherwise indicate high probability of disease and justify imaging for a tumour.

Consensus point

(9) With some exceptions, plasma metanephrines in excess of twice the upper reference limit indicate a high likelihood of a PPGL and the patient can proceed to imaging studies.

IMAGING OF PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

Imaging of patients with a PPGL is important at every step of their management. Anatomic imaging by contrast-enhanced computed tomography (CT) or MRI is usually

sufficient to locate a tumour and proceed to surgery. However, combined with functional imaging, there is added value in improved specificity, sensitivity (detection of metastases and multifocality) and links with targeted radionuclide therapy. The optimal choice of a radiopharmaceutical depends heavily on tumour genotype and biology, which are linked to location (sympathetic versus parasympathetic, adrenal versus extra-adrenal), size and biochemical phenotype as detailed in the recently updated European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 (Table 3) [51].

Phaeochromocytomas

The radiological appearance of PPGLs on anatomical imaging is variable. Phaeochromocytomas can be homogeneous or heterogeneous, including features of necrosis, haemorrhage, cystic changes and calcifications. In representative areas of the tumour, however, unenhanced attenuation on CT is almost invariably more than 10 Hounsfield units as opposed to most adrenal adenomas [33,35,52]. Contrast washout is unreliable in an individual patient to distinguish between phaeochromocytoma and adenoma. On MRI, a high-intensity (bright) T2-weighted signal is typical for phaeochromocytoma, but this occurs in only one-third of tumours [53,54].

Additional functional imaging can be useful in patients with bilateral masses or a high risk of multifocality (e.g. due to a hereditary syndrome) or in a critical care setting and renal insufficiency. ^{18}F -FDOPA PET, ^{68}Ga -DOTA-somatostatin analogue (SSA) PET might then be performed [12,51] (Table 3). When PET is unavailable, ^{123}I -MIBG scintigraphy can be a next alternative, though with recognition that its impact on clinical decision making is limited [55–57]. Functional imaging is also recommended for excluding metastatic disease particularly in large phaeochromocytomas (>5.0 cm) and in patients with *SDHA/B/D* mutations. In these cases, ^{68}Ga -DOTA-SSA PET can be performed depending on the genotype.

There are several typical locations for extra-adrenal paragangliomas: the peri-aortic region, particularly the Zuckerkandl body as an example of a paraganglion located at the root of the inferior mesenteric artery; the sympathetic plexus of the urinary bladder, the kidneys and the heart; and alongside the sympathetic ganglia in the posterior mediastinum. For such tumours, it is important to exclude other neurogenic tumours, sarcomas and pathologically enlarged lymph nodes. The specificity of functional

TABLE 3. Proposed clinical algorithm for nuclear imaging investigations in pheochromocytoma and paraganglioma

	First choice	Second choice	Third choice
Pheochromocytoma (sporadic)	^{18}F -FDOPA or ^{123}I -MIBG	^{68}Ga -DOTA-SSA	^{18}F -FDG
Hereditary pheochromocytoma (except SDHx): NF1/RET/VHL/MAX	^{18}F -FDOPA	^{123}I -MIBG or ^{68}Ga -DOTA-SSA	^{18}F -FDG
Extra-adrenal sympathetic and/or multifocal and/or metastatic and/or SDH mutation	^{68}Ga -DOTA-SSA	^{18}F -FDG and ^{18}F -FDOPA	^{18}F -FDG and ^{123}I -MIBG or ^{18}F -FDG and ^{111}In -SSA/ $^{99\text{m}}\text{Tc}$ -SSA
Head and neck paraganglioma (sporadic)	^{68}Ga -DOTA-SSA	^{18}F -FDOPA	^{111}In -SSA/ $^{99\text{m}}\text{Tc}$ -SSA

Adapted from the 2019 EANM/SNMMI guidelines [51].

imaging together with metanephrines is helpful in this respect. In patients with confirmed or suspected *SDH* mutations, ^{68}Ga -DOTA-SSA is the imaging modality of choice (Table 3). When PPGL is caused by *VHL* or *HIF2A* mutations, ^{18}F -FDOPA appears to be superior to ^{68}Ga -DOTA-SSA [58,59].

Head and neck paragangliomas

Functional imaging is highly sensitive for detecting multiple tumours and facilitates their subsequent location by anatomical imaging with dedicated protocols. On the basis of the most recent studies, ^{68}Ga -DOTA-SSA is today considered the first-choice radiopharmaceutical [56,60–62]. Anatomic imaging with MRI and temporal bone CT serves as the first-line approach for locoregional staging. MR angiography sequences are particularly sensitive for detecting tumours, especially 3D time-of-flight and 4D MR acquisitions [56,63].

Consensus points

(12) Nearly all pheochromocytomas have unenhanced attenuation on CT (>10 Hounsfield units; Contrast washout is unreliable in an individual patient to distinguish between pheochromocytoma and adenoma.

(13) Functional imaging is essential in patients with a high risk of recurrence or multifocal disease.

(14) The optimal choice of the radiopharmaceutical for functional imaging depends on genotype, biochemical phenotype, size and location.

(15) MRI angiography and ^{68}Ga -DOTA-SSA PET are considered as first-choice imaging modalities in patients with HNPGLs.

METASTATIC PHAEOCHROMOCYTOMAS AND SYMPATHETIC PARAGANGLIOMA

The excellent results obtained with ^{68}Ga -DOTA-SSA PET in sporadic and SDH-related PPGL have simplified the imaging approach to patients with metastatic disease [64–67]. ^{68}Ga -DOTA-SSA PET/CT is also very useful for follow-up and assessment of responses to therapies, complementary to anatomic imaging that remains the gold standard (RECIST evaluation). ^{18}F -FDG and ^{18}F -FDOPA PET may serve as alternatives in this setting (Table 3). ^{68}Ga -DOTA-SSA or ^{123}I -MIBG can also be used for selecting patients for targeted radionuclide therapy with ^{177}Lu -DOTATATE or ^{131}I -MIBG, respectively.

Consensus point

(16) ^{68}Ga -DOTA-SSA PET imaging is the preferred imaging modality in patients with metastatic disease and is mandatory for selecting patients amenable for ^{177}Lu -DOTATATE treatment.

GENETICS

PPGL has the highest known heritability rate among all human tumours. Up to 40% of patients with this disease carry germline mutations in one of the 25 known susceptibility genes, a proportion that increases every year as mutations impacting new genes are found. Somatic mutations in some of the same genes or other genes known to initiate tumorigenesis can be found in an additional 30–40% of patients with sporadic disease (Supplemental Table 2, <http://links.lww.com/HJH/B310>) [68–71]. Genetic alterations as a whole therefore currently explain up to 80% of all cases. Other somatic mutations, such as in *ATRX* and *TERT* genes, may have a secondary role in influencing disease progression with potential prognostic significance. On the basis of these and other accumulating data, it is recommended to consider genetic studies for any patient diagnosed with PPGL [72,73].

Although genetic testing has traditionally been performed on DNA acquired from blood or buccal swabs, recent data suggest a potential benefit of PPGL mutational screening on tumour DNA (conveniently selected by a pathologist in order to avoid excessive contamination with normal tissue) [74,75]. If a mutation in the tumour is found, the second step is to search for that same unique mutation in germline DNA. This not only enables discrimination of inherited from sporadic disease but also allows for targeted germline testing, and as detailed later, the available tumour material can also help to determine the pathogenicity of variants of unknown significance. Although somatic genetic testing has yet to be routinely employed, it should become the future procedure of choice for any index patient in whom tumour material is available.

Late age of onset or the lack of family history of the disease does not exclude a germline mutation [74,75]. This mainly reflects the low penetrance of some gene mutations such as those of *SDHA* [76] and to inheritance models modified by imprinting or other mechanisms, which result in generation-skipping of clinical manifestations of the disease for a specific gene. This, for example, is the case for *SDHD* [77]. Although paediatric cases usually involve germline mutations, for those presenting with a single tumour more than 20% are explained by somatic mutations [74,75].

It is recommended that all patients with PPGL be engaged in shared decision making for genetic testing [12]. There is a long list of known PPGL driver genes, the most prevalent include *SDHB*, *SDHD*, *VHL*, *RET* and *NF1* with lower prevalences for *SDHA*, *SDHAF2*, *MAX*, and

TMEM127 (Supplemental Table 2, <http://links.lww.com/HJH/B310>). Mutations in the *SDHB* gene are associated with the highest risk of metastatic disease (30–70%). For the other most common genotypes (e.g. *RET*, *NF1*, *VHL*), metastatic risk is substantially lower (<5–10%) than associated with *SDHB* mutations. However, for some rare genotypes (*SDHA*, *SDHC*, *FH*, *MDH2*, *SLC25A11*), there is emerging evidence that metastatic risk may be higher than 10%. The clinical presentation of a patient does not always predict the underlying genotype [74,75]; thus, a gene by gene screening is not always the most effective and efficient path for identifying mutations. Instead, targeted next-generation sequencing (NGS) is now the recommended approach by enabling testing of all relevant genes in a single panel [78].

The information from the genetic test is critical not only to the patient but also to the relatives who may carry the same germline mutation; thus, genetic screening for the same mutation should be offered to family members at risk for the mutation. In such cases, the minimum age for performing genetic testing should be performed depending on the specific causal gene and nature of surveillance indicated for mutation carriers. Although this age is well established at 5 years for *VHL* syndrome [79], there remains debate for other hereditary causes of PPGL. On the basis of a review of the literature comprising 105 paediatric cases, the proposed minimum age for starting genetic testing is 5 years for *SDHB* and 10 years for *SDHA*, *SDHC* and *SDHD*-related PPGLs [80].

Although NGS carries advantages over former methods for genetic diagnosis, it also generates large amounts of data in need of interpretation [81]. In particular, although many genetic variants have been characterized, others are inevitably classified as variants of unknown significance (VUS). Suspicion of a VUS requires complementary testing to establish whether a mutation is pathogenetic (Supplemental file §2, <http://links.lww.com/HJH/B310>).

Consensus points

- (17) Currently, nearly 80% of all PPGLs can be explained by genetic alterations, and therefore, all patients with a PPGL should be considered for genetic testing.
- (18) Lack of family history for PPGL does not preclude the presence of a germline mutation.
- (19) NGS is the preferred technique to analyse all relevant genes in a single test.
- (20) Suspicion of a variant of unknown significance requires complementary testing to establish whether a mutation is pathogenetic.

PRESURGICAL AND SURGICAL MANAGEMENT OF PHAEOCHROMOCYTOMA AND PARAGANGLIOMA

Treatment of patients with a PPGL requires a multidisciplinary team of dedicated specialists in centres that have extensive experience in management of these complex patients. This approach ensures the most favourable outcome [12].

Surgical resection is the only curative treatment for PPGL. Surgery itself, however, may evoke a massive release of catecholamines from a PPGL into the circulation, resulting in potentially life-threatening cardiovascular

complications, including hypertensive crises, cardiac arrhythmias, myocardial infarction, pulmonary oedema and multiorgan failure [82,83]. In addition, the rapid drop in catecholamines after resection of the PPGL may result in severe hypotension [84]. For prevention of these cardiovascular complications, treatment with antihypertensive drugs before surgery is recommended [12]. Even though the evidence underpinning these recommendations for optimal presurgical treatment is almost entirely based on observational studies and expert opinion, the published studies that question this approach do not provide sufficient solid evidence that surgery without appropriate presurgical preparation is well tolerated and feasible [85–87].

Presurgical administration of α -adrenergic receptor blockers is considered as the treatment of first choice [12]. Frequently prescribed drugs are phenoxybenzamine, a nonselective and noncompetitive α_1 and α_2 -adrenergic receptor blocker, or doxazosin, a selective and competitive α_1 -adrenergic receptor blocker. These drugs (dosed twice daily) are initiated at least 7–14 days before surgery in gradually increasing dosages until blood pressure targets are achieved (distinct recommendations on drug dosing can be found elsewhere, e.g. [12]). Retrospective studies comparing the efficacy of these two α -adrenergic receptor blockers have yielded conflicting results [88–91]. The only randomized controlled trial comparing presurgical treatment with either phenoxybenzamine or doxazosin did not find any difference in the total duration of blood pressure levels outside the predefined target range during surgery [92]. It was found, however, that phenoxybenzamine was associated with more hemodynamic stability during surgery [92]. Although there is no consensual definition of hemodynamic instability, several studies have demonstrated that hemodynamic instability is associated with a higher risk of adverse perioperative events [93–95]. It should be noted that normotensive patients with a PPGL with normal or elevated levels of catecholamines or metanephrines may also be at an increased risk of intraoperative haemodynamic instability and should therefore receive presurgical α -blockade as well [96,97].

Calcium channel blockers may be added to an α -adrenergic receptor blocker for further improvement of blood pressure control [21,90,92]. These drugs have also been used as the treatment of first choice for presurgical management in patients with PPGL [98,99], but α -adrenergic receptor blockers should be preferred. In general, however, calcium channel blockers are not recommended as monotherapy unless in case of normal or mildly elevated preoperative blood pressure levels or severe orthostatic hypotension during α -adrenergic receptor blocker [12].

Presurgical treatment with β -adrenergic receptor blockers is required for presentations of tachycardia, which can be a direct result of catecholamine hypersecretion by the PPGL or occur as reflex tachycardia after the initiation of α -adrenergic receptor blockers. It is of utmost importance that treatment with β -adrenergic receptor blockers should only be initiated in a patient already receiving an α -adrenergic receptor blocker; if not, there is risk of a hypertensive crisis due to unopposed stimulation of α -adrenergic receptors with ensuing peripheral vasoconstriction [100].

The optimal presurgical blood pressure and heart rate targets have not been established firmly, as no randomized comparative studies have been conducted. A seated blood pressure target less than 130/80 mmHg and an upright SBP more than 90 mmHg have been suggested previously [12]. The last recommendation has been corroborated by the finding that an upright SBP less than 90 mmHg was associated with more haemodynamic instability [91,92]. Suggested heart rate targets are 60–70 and 70–80 bpm in seated and upright position, respectively [12].

Mortality rates for PPGL resection have dropped impressively from about 40% in the past to 0–3% in contemporary series [92,93,101,102]. It is likely that the improved perioperative outcome is the combined result of presurgical administration of α -adrenergic receptor blockers and major technical advances in both anaesthesiology and surgery. In view of their efficacy in controlling catecholamine-induced symptoms and signs, minimal side effects and the lack of randomized placebo-controlled trials, α -adrenergic receptor blockers remain the mainstay of presurgical medical treatment.

It is advised to use a high-sodium intake during treatment with α -adrenergic receptor blockers in order to reduce the risk of orthostatic hypotension before surgery and hypotension during the postoperative period [12]. In addition, intravenous administration of 1–2 l of saline during the last 24 h of surgery is commonly performed [12,21,103]. Supportive evidence for this practice is limited and based on a few retrospective studies [104,105].

Minimally invasive adrenalectomy is the preferred surgical approach [106]. Transabdominal laparoscopic and retroperitoneoscopic adrenalectomy are the most frequently used techniques. The surgical approach does not significantly affect the intraoperative haemodynamics [107]. Minimally invasive adrenalectomy is associated with lower blood loss and shorter postoperative length of stay than open adrenalectomy [108,109].

In patients with some hereditary syndromes such as MEN2, partial adrenalectomy should be considered, as this can preserve adrenocortical function, thus circumventing steroid replacement [110]. In patients in whom extensive surgery results in bilateral adrenalectomy, adequate steroid replacement should be initiated in a timely manner.

Head and neck paragangliomas

As most HNPGLs do not synthesize significant amounts of catecholamines, only patients with elevated metabolites of one or more catecholamines should have presurgical adrenergic blockade. It has to be noted that there is no strong scientific evidence for this approach.

Although surgery is the only curative treatment option for HNPGLs, radical surgical resection is not always possible or is not the preferred option. Advanced tumours, as stratified by specific radiological classification systems, may encroach adjacent structures and removal may therefore cause potentially serious complications. Options other than surgery that might be considered are wait-and-scan, stereotactic radiosurgery and conventional radiotherapy or more recently somatostatin-receptor directed targeted radiotherapy for progressive locally advanced tumours [31,111,112].

Patient-tailored treatment decisions should be reached in a multidisciplinary setting and requires optimal localisation and staging, knowledge of the genetic status and disease course [31].

Consensus points

(21) Presurgical medical preparation using an α -adrenergic receptor blocker remains the mainstay for preventing life-threatening perioperative cardiovascular complications.

(22) Normotensive patients with a PPGL should also receive presurgical medical treatment, as they are also at an increased risk of haemodynamic instability.

(23) In patients with HNPGLs, presurgical adrenergic blockade is only indicated in patients with positive biochemistry.

(24) Both doxazosin and phenoxybenzamine are effective for preoperative treatment.

(25) β -adrenergic blockade for treatment of tachyarrhythmias should not be started before instalment of α -adrenergic blockade.

(26) Minimally invasive adrenalectomy is the preferred surgical approach.

POSTSURGICAL FOLLOW-UP

Surgical resection of a PPGL does not guarantee cure. There may be residual tumour tissue, another PPGL or distant metastases. Even when surgery results in complete resection, there remains risk of local recurrence, metastatic recurrence or a new PPGL. Thus, postsurgical follow-up and continued surveillance is essential [13].

For the patients with residual disease, including metastasis, the nature of postsurgical follow-up and the frequency of clinical, biochemical and imaging follow-up is best established by a multidisciplinary team and specially the physician in charge of the patient.

For patients who have undergone surgery, the first issue is to establish whether surgical resection was complete. The European guideline recommends measurements of metanephrine, normetanephrine and 3-methoxytyramine 2–6 weeks after recovery from surgery according to the nature of elevated concentrations before surgery (Fig. 1) [13]. Earlier measurements after surgery can also be informative. Metanephrines in the normal range after surgery document complete resection and no anatomical imaging is required [40]. In cases of postsurgically elevated metanephrines or of a nonfunctional PPGL, imaging may be performed 3 and 6 months after surgery to document completeness of resection [13].

If the patient is tumour free at postoperative evaluation, an explanation for the need and nature of follow-up should be provided for the patients. Patients should first be informed that there is a small risk of malignancy and that disease cannot distinguish benign and metastatic PPGL. In addition, information should be provided about any results of genetic testing that may contribute further to need for follow-up.

Risk of recurrence has been described to be one per 100 person-years [113], with further doubling of risk in patients with genetic or syndromic disease [113]. Although follow-up is recommended for all patients, studies establishing any impact of follow-up on outcomes are scarce. Nevertheless, there is consensus that follow-up should be performed in all patients during the first 10 years after surgery. Available data are insufficient to assess any potential values of postsurgical follow-up beyond 10 years. For patients with

FIGURE 1 >Flow chart for guiding follow-up after surgery (adapted from [13]). After 10 years of follow-up, there are insufficient data to provide any recommendation about follow-up of patients with a sporadic small (<5 cm) pheochromocytoma. Young patients or patients with a sympathetic paraganglioma, a mutation or a large tumour (≥ 5 cm) should have lifelong follow-up. Metanephrines: normetanephrine, metanephrine (plasma or urine). BP, blood pressure; CgA, chromogranin A; PGL, sympathetic paraganglioma; Pheo, pheochromocytoma.

functional PPGLs, it is commonly accepted that follow-up should include clinical examination and annual assessment of metanephrines (Fig. 1). For patients in whom primary tumours were nonfunctional (e.g. HNPGLs), it is proposed that imaging studies should be performed every 2 years.

Depending on presentation, there is considerable scope for personalized approaches to follow-up. Patients with large tumours, paragangliomas, a childhood presentation, multifocal disease or *SDHB* mutations have a high risk for metastatic progression [114–116]. These patients may particularly benefit from long-term and more strict annual surveillance, including measurements of plasma 3-methoxytyramine, in order to detect recurrent disease at an earlier stage amenable to therapeutic intervention. For all patients at hereditary risk such as VHL or SDHx syndrome, there is need for annual surveillance with measurements of catecholamine O-methylated metabolites that can be individualized according to genotype-phenotype relationships as well as any additional syndromic features.

Consensus points

- (27) All patients who have been operated for a PPGL should be followed up annually for at least 10 years.
- (28) Follow-up should at least include assessment of symptoms, blood pressure and plasma or urinary-free metanephrines.
- (29) The first follow-up should be at 2–6 weeks after surgery to verify completeness of surgical resection. In case of persistent abnormal biochemical test results, imaging studies are indicated.
- (30) Patients at high-risk for recurrent disease such as the young individuals, those with a paraganglioma, germline mutation, and patients with a large tumour, should be followed up lifelong.

METASTATIC PHAEOCHROMOCYTOMA/ PARAGANGLIOMA

Metastatic PPGL is defined by the occurrence of metastatic lesions either in lymph nodes or bones, lung or liver (WHO) [117]. Approximately 10–20% patients with these tumours develop metastatic lesions, about 10–15% at initial diagnosis of the primary tumour [118]. About half of patients with metastatic disease harbour PPGL susceptibility genes mutations, most frequently *SDHB*, and 50–70% will be considered as apparently sporadic [118,119]. More than 90% of these PPGLs are functional, with most of them having a noradrenergic and/or dopaminergic phenotype [71,115,120].

Clinically, patients with metastatic PPGL usually present similarly as patients with nonmetastatic PPGL. However, due to a high tumour burden, many patients present with severe hypertension or fluctuation of blood pressure due to episodic catecholamine secretion from metastatic lesions; associated with this there may be catecholamine-induced end-organ dysfunction (e.g. ileus, severe constipation, organ ischemia, drug-resistant hypertension and tachyarrhythmia) [121]. Although the development of metastatic PPGL cannot be predicted by a magic circulating biomarker, large tumour size (>5 cm), extra-adrenal location, multifocality, dopaminergic biochemical phenotype, are risk factors for metastatic disease that are also linked to underlying genetic risk [118–120,122]. Metastatic behaviour of the most aggressive *SDHB*-related PPGLs is associated with their specific mutation types and the size of the primary tumour. Meanwhile, the age at initial diagnosis, functional phenotype and the presence of multiple tumours or metastatic disease predict overall survival [120].

Treatment options for metastatic PPGLs are limited but require personalized considerations. Before any treatment of metastatic PPGL is initiated, a physician must perform appropriate staging of disease and establish disease progression (usually by imaging over a 3-month interval). Exceptions involve patients with numerous liver, lung and brain metastatic lesions in whom therapy should be initiated immediately. In patients with rapidly progressive disease, chemotherapy is preferable. Classic CVD (cyclophosphamide, vincristine, dacarbazine) chemotherapy may be effective, especially in patients harbouring *SDHx* gene mutations: up to 70% of patients will respond compared with 30% with apparently sporadic PPGL [123–126]. Other approaches include temozolomide, temozolomide together with capecitabine, temozolomide with PARP inhibitors, tyrosine kinase inhibitors and cold SSAs (for review, see Nölting *et al.* [127]).

For moderately progressive metastatic disease, radiotherapeutic approaches should be considered; these include ^{177}Lu -DOTATATE (Lutathera) and ^{131}I -MIBG, the latter either high-specific-activity ^{131}I -MIBG (Azedra) or conventional ^{131}I -MIBG [128–131]. Present data suggest that efficacy of Azedra and Lutathera is similar, around 90% [111]. External beam radiation is used especially for metastatic bone lesions and to alleviate pain or to treat lesions associated with possible spinal cord compression [127]. All patients with metastatic PPGL require lifetime follow-up including annual measurements of metanephrines and restaging using either anatomic or functional imaging modalities. This follow-up frequency may be altered and can be much shorter depending on tumour burden, disease progression and the patient's clinical presentation.

Personalized management of metastatic PPGL and future directions of research

For metastatic disease, we have witnessed new molecular subclassification of these tumours, involving the Wnt pathway, *MAML3* fusion and *CSDE1* genes. Larger-scale studies, some by utilizing the sophisticated link between TCGA/other databases and available bioinformatics tools, discovered clearer predictors of metastatic disease [73,132]. These include the *ATRX* and *SDHB* mutations as well as telomerase activation or *TERT* structural rearrangement [133].

The immediate future directions of research tightly linked to clinical practice more than ever before will require multi-institutional and large-scale collaborations in order to obtain solid, usable and easily transferable results to patients. Promising uses of PARP inhibitors together with temozolomide, bone seeking calcium mimetic alpha emitter ($^{223}\text{RaCl}_2$; Xofigo), various approaches for somatostatin receptors-targeted radiotherapy, immunotherapy and radioimmunotherapy are on the horizon [134]. In the near future, treatment options will also take advantage of new schedules, timing paradigms, potential synergistic combinations, new bioinformatics tools and artificial intelligence. Furthermore, the search has already begun to discover new targets, biomarkers, oncometabolites, lincRNAs and signalling pathways that can be used for tumour identification,

pathogenesis, localization and treatment. Precision medicine recommendation cards, especially for rare tumours, will soon be available to practicing physicians.

Consensus points

(30) *SDHx* mutations, tumour size larger than 5 cm, multifocality and dopaminergic biochemical phenotype are risk factors for developing metastatic disease.

(31) Forty to 50% of patients with metastatic PPGL harbour *SDHx* mutations.

(32) Staging of metastatic PPGL should first be carried out using ^{68}Ga -DOTATATE PET/CT.

(33) Rapidly progressing metastatic PPGLs should be treated with chemotherapy (CVD preferable); slowly growing ones can be treated with radiotherapy using either Lutathera or ^{131}I -MIBG therapy.

PERSONALIZED MANAGEMENT

The diagnosis, management and therapy of patients with PPGL can benefit from personalized approaches requiring close multidisciplinary clinical teams of endocrinologists or internists, geneticists, clinical chemists, radiologists, specialists in nuclear medicine, surgeons, pathologists and when needed oncologists. Only working together in such teams can patients with PPGLs receive optimal personalized care at each step in their management journey from initial testing to surgical intervention and follow-up or treatment of metastatic disease. As outlined in the preceding sections, such personalized care starts with consideration of the actual presentation of the patient, according to specific signs and symptoms, findings of an incidentaloma or if testing is carried out as part of surveillance due to hereditary risk or previous disease. From individualized assessments of disease risk and subsequent biochemical test results, patients can be stratified according to posttest probabilities of disease for immediate imaging studies, further evaluation or exclusion of a tumour. As also outlined, major advances in genomics have revealed the rich hereditary background of PPGLs that has been instrumental in guiding personalized approaches to biochemical testing, imaging studies, therapeutic interventions and disease follow-up. Genomic information is now also allowing us to identify specific tumourigenic pathways, relevant for development of potential therapeutic targets for metastatic or inoperable PPGL. We are now at a critical cross-road where clinicians who first see these patients, such as those involved in hypertension care, should be aware of progress in the field and best approaches to provide optimal management of their patients in whom PPGLs are detected.

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Conflicts of interest

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