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Update on Modern Management of Pheochromocytoma and Paraganglioma

Jacques W. M. Lenders[1,2], Graeme Eisenhofer[2,3]

[1]Department of Internal Medicine, Radboud University Medical Center, Nijmegen, The Netherlands; [2]Department of Medicine III, [3]Institute of Clinical Chemistry and Laboratory Medicine, University Hospital and Medical Faculty Carl Gustav Carus, Dresden University of Technology, Dresden, Germany

Despite all technical progress in modern diagnostic methods and treatment modalities of pheochromocytoma/paraganglioma, early consideration of the presence of these tumors remains the pivotal link towards the best possible outcome for patients. A timely diagnosis and proper treatment can prevent the wide variety of potentially catastrophic cardiovascular complications. Modern biochemical testing should include tests that offer the best available diagnostic performance, measurements of metanephrines and 3-methoxytyramine in plasma or urine. To minimize false-positive test results particular attention should be paid to pre-analytical sampling conditions. In addition to anatomical imaging by computed tomography (CT) or magnetic resonance imaging, new promising functional imaging modalities of photon emission tomography/CT using with somatostatin analogues such as ^{68}Ga-DOTATATE (^{68}Ga-labeled DOTA(0)-Tyr(3)-octreotide) will probably replace ^{123}I-MIBG (iodine-123-metaiodobenzylguanidine) in the near future. As nearly half of all pheochromocytoma patients harbor a mutation in one of the 14 tumor susceptibility genes, genetic testing and counseling should at least be considered in all patients with a proven tumor. Post-surgical annual follow-up of patients by measurements of plasma or urinary metanephrines should last for at least 10 years for timely detection of recurrent or metastatic disease. Patients with a high risk for recurrence or metastatic disease (paraganglioma, young age, multiple or large tumors, genetic background) should be followed up lifelong.

Keywords: Pheochromocytoma; Paraganglioma; Catecholamines; Metanephrine; Adrenal

INTRODUCTION

Pheochromocytoma and paraganglioma (PPGLs) are rare chromaffin cell tumors with a variable prevalence depending on the investigated population. In patients with hypertension the prevalence of a PPGL is about 0.2% to 0.6% while in patients with an incidentally discovered adrenal tumor it is about 3% to 7% [1-3]. Physicians are apprehensive to miss this tumor because it is associated with significant cardiovascular morbidity and catastrophic consequences when the diagnosis is overlooked [4-7]. Yet, the average delay in the diagnosis is nearly 3 years and it is even missed during life in 0.05% to 0.1% of the patients as shown by autopsy studies [1].

Both PPGLs are chromaffin cell tumors that arise from the adrenal medulla (80% to 85%) or from the ganglia of the sympathetic chain in thorax, abdomen, and pelvis (15% to 20%) [8]. Paragangliomas located in the head and skull base areas a have a parasympathetic origin [9,10]. In terms of biochemical pheno-

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Corresponding author: Jacques W. M. Lenders
Department of Internal Medicine, Radboud University Medical Center, PO Box 9101, 6500HB, Nijmegen, The Netherlands
Tel: +31-243618819, **Fax:** +31-243541734,
E-mail: Jacques.lenders@radboudumc.nl

type, adrenal tumors produce epinephrine with a varying amount of norepinephrine. Half of all adrenal tumors have an adrenergic biochemical phenotype while the other half have a noradrenergic phenotype [11]. Extra-adrenal tumors (paragangliomas) arising from sympathetic ganglia have a noradrenergic phenotype, producing predominantly or exclusively norepinephrine. Head and skull base paragangliomas usually do not produce catecholamines except for some dopamine and its metabolite 3-methoxytyramine. PPGLs in childhood have a preponderance of extra-adrenal and multifocal tumors and carry an increased prevalence of mutations in one of the PPGL susceptibility genes [12].

The classical signs and symptoms of PPGLs are well known but unfortunately are not very specific since they resemble those of many other clinical conditions, in particular disorders associated with increased sympathetic activity. The episodic nature of catecholamine secretion is the basis for the paroxysmal nature of signs and symptoms, including severe blood pressure fluctuations [1,13,14]. Any paroxysmal signs or symptoms should be a compelling clue to consider the presence of a PPGL. Due to the combination of rarity and multifaceted presentation of these tumors the diagnosis of PPGLs is not always straightforward. Recently, the indications for screening for PPGLs have been updated (Table 1) [15].

Malignant PPGL is characterized by metastases of chromaffin tissue in locations that are normally devoid of chromaffin tissue, such as bones, lungs, and liver. The overall prevalence of metastatic disease among patients with PPGLs is 10% to 15%, but may amount to 30% to 40% in the presence of specific risk factors: young age, genetic background in particular succinate dehydrogenase B (SDHB) mutations, large tumor size, dopaminergic phenotype, multifocal tumors, and extra-adrenal location [16,17].

Table 1. Indications for Biochemical Testing for Pheochromocytoma/Paraganglioma

Signs or symptoms suggesting catecholamine excess, in particular if paroxysmal
Unexpected blood pressure response to drugs, surgery, or anesthesia
Unexplained blood pressure variability
Incidentaloma, also in normotensive patients
Difficult to control blood pressure
Previous treatment for pheochromocytoma or paraganglioma
Hereditary risk of pheochromocytoma or paraganglioma in family members
Syndromic features relating to a pheochromocytoma-related hereditary syndrome

Adapted from Lenders et al. [15].

PRACTICAL APPROACH TO THE BIOCHEMICAL DIAGNOSIS

An essential prerequisite prior to ordering biochemical testing are a thorough medical history including a family history and assessment of factors that may provoke paroxysms such as certain drugs [1,18]. At physical examination special attention should be paid to proper blood pressure measurements. Ambulatory 24-hour measurements are not only a more objective assessment of blood pressure but also allow assessment of exceptional blood pressure variability. As PPGL may be part of several hereditary syndromes (e.g., von Hippel-Lindau [VHL] disease and multiple endocrine neoplasia type 2 [MEN2] syndrome), one has to be attentive to other overt or hidden features of these syndromes [19-21]. This aspect of the work-up is not only very relevant for appropriate interpretation of biochemical test results but it also impacts on further more personalized management strategy.

In case of clinical suspicion of a PPGL, the next diagnostic step is biochemical testing. Evidence of excess production of catecholamines or the O-methylated catecholamine metabolites, metanephrines, is in general a condition *sine qua non* before proceeding to more expensive imaging procedures. According to the recommendations of the recent Endocrine Society guideline, initial biochemical testing for PPGLs should include measurements of plasma free or urinary metanephrines [15]. Plasma free metanephrines combined with the dopamine metabolite 3-methoxytyramine offer a slightly higher sensitivity (99%) than that of urinary deconjugated metanephrines (95%). The nearly maximal negative predictive value of plasma free metanephrines indicates that a pheochromocytoma or paraganglioma can be considered as excluded with a high reliability when the test result is within the normal range [22]. This even applies at very low pretest probability of disease (0.2% to 0.6%), as is the case in asymptomatic hypertensive patients [23]. Exceptions are rare patients with biochemically silent tumors who carry an SDHB mutation [24]. Elevated levels of 3-methoxytyramine may be associated with metastatic disease or can be found in patients with neck and skull base paragangliomas. The very high diagnostic sensitivity of metanephrines is due to the continuous diffusion of intratumorally-produced metanephrines into the circulation, which contrasts with the episodic secretion

of the parent catecholamines [25]. In addition, measurements of plasma metanephrines result in less false-positive test results than those of urinary metanephrines with specificities of 96% and 89%, respectively.

For reliable measurement of metanephrines and interpretation of test results, preanalytical conditions need consideration. No dietary restrictions are needed for measurements of plasma metanephrines except for dietary use of amine rich foods, which might result in false-positive test results for 3-methoxytyramine [26]. Therefore, blood sampling in the fasting state is advised to minimize the risk of false-positive test results. Blood samples for measurements of plasma metanephrines (collected in heparinized tubes or tubes with ethylenediaminetetraacetic acid) need to be placed immediately on ice to prevent degradation. If samples are assayed within 30 days, storage of plasma at –20°C is sufficient [27]. For measurement of urinary metanephrines, no special dietary precautions need to be taken and containers do not need additives as long as the urine sample is acidified (pH 4) before storage [28]. To verify complete 24-hour urine collection, simultaneous measurement of urinary creatinine excretion is useful.

Several sympathetic stimuli such as stress and upright body position may increase plasma metanephrines and this will impact test results. Conversely, taking blood samples in the supine position will on average result in 30% lower plasma normetanephrine values as compared to the sitting position. Therefore venous blood samples for metanephrines should preferentially be taken after supine rest for at least 20 minutes. This will further minimize the risk of false-positive test results. A recent systematic review showed a higher sensitivity of plasma metanephrines if blood samples are taken after supine rest than of samples taken in the seated position without rest [29]. If drawing blood samples after supine rest is not operational in medical facilities, measurement of 24-hour urinary metanephrines is an acceptable alternative.

Before starting biochemical testing, one has to consider false-positive test results related to the use of specific drugs that can cause analytical or pharmacological interference [15]. In case of measurements by mass spectrometric methods such as LC-MS/MS (liquid chromatography with tandem mass spectrometry), analytical interference is negligible as compared to high pressure liquid chromatography with electrochemical detection. Pharmacodynamic interference is still possible as this is assay independent. Typical examples of drugs to consider in case of elevated test results are tricyclic antidepressants and sympathomimetic drugs. In cases in which it is not possible to interrupt such drugs temporarily, the clinician has a diagnostic dilemma and is left with proceding to imaging as the only way out.

As usual for diagnostic testing in general, one has also to consider the clinical context of the patient, including the pretest probability of disease [23]. Increased sympathetic activity is a distinctive hallmark of many co-existent conditions. Such comorbidities accompanied by strong elevations of sympathoneural activity are a source of falsely-elevated plasma normetanephrine levels. Typical examples are occult or overt heart failure or life threatening conditions at the intensive care unit [30]. More pronounced elevations of plasma metanephrine can occur during severe pain as is the case during cardiac ischemia or hypoglycemia. Consequently, in life threatening stressful conditions, as is the case in patients on intensive care units, a reliable biochemical diagnosis is not feasible and the next best test to rule out PPGL is imaging.

For correct interpretation of test results, one has to consider appropriate reference intervals and cut-off values. Preferably laboratories should establish or verify their own reference values. Three important considerations should be noted: first, reference values should be established from subjects who are sampled after supine rest. This reduces the risk of missing a PPGL. Second, the ideal reference population consists of patients who were suspected for a PPGL but in whom a PPGL was ruled out. Finally, reference values for plasma normetanephrine should be adjusted for age while this is not necessary for metanephrine and 3-methoxytyramine (Table 2). Although plasma metanephrines and 3-methoxytyramine are slightly higher in males than in females, no gender specific cut-off reference values are required in clinical care.

Paying insufficient attention to how blood is collected and how results are interpreted might explain the high rates of misdiagnosis, in particular of false-positive test results of up to 20%, as reported from an academic hypertension clinic [31]. If

Table 2. Age-Related Upper Cut-off Values for Plasma Metanephrines and 3-Methoxytyramine

Age, yr	Normetanephrine, nmol/L	Metanephrine, nmol/L	3-Methoxytyramine, nmol/L
5–17	0.47	0.45	0.10
18–29	0.58	0.45	0.10
30–39	0.70	0.45	0.10
40–49	0.79	0.45	0.10
50–59	0.87	0.45	0.10
>60	1.05	0.45	0.10

testing returns positive results for plasma or urinary metanephrines, it is useful to ask yourself the following questions: is blood or urine sampling carried out correctly?; does the patient use potentially interfering medications?; does the patient suffer from comorbidity; or is there another reason for increased sympathetic activity that might explain the test result?

Finally, for correct interpretation of test results one has to take into account pretest probability of disease and the extent of elevation over the upper cut-off value [23]. Increment of plasma metanephrines well in excess of 2-fold the upper cut-offs provides a high level of confidence that the patient has a PPGL since such increments are very rare in patients without a PPGL. In these patients the diagnostic step is to locate the tumor using imaging. In patients with slightly elevated test results (<2-fold the upper cut-off), it is difficult to distinguish false-positive from true-positive test results. Such patients, in particular when the clinical suspicion is low, can be monitored by biochemical follow-up to gauge a potentially further increase in plasma metanephrines. If clinical suspicion is moderate or high and plasma normetanephrine is elevated, a clonidine suppression test is useful to exclude the tumor [32].

IMAGING STRATEGIES

Once a biochemical diagnosis of a catecholamine producing tumor has been established, the next step is to localize the tumor by anatomical imaging. Exceptions are critically ill patients in emergency situations where imaging has priority over biochemical testing since a reliable and rapid biochemical diagnosis is not feasible [30]. Computed tomography (CT) scanning is the preferred imaging modality because its outstanding spatial resolution is superior to that of magnetic resonance imaging (MRI). MRI is reserved for patients with the following conditions: metastatic disease, intracardiac or skull base and neck paragangliomas, postoperative surgical clips, allergy to CT contrast, and in those conditions in whom radiation exposure should be limited: children, pregnant women, and patients with known germline mutations [15]. The abdominal and pelvic areas are the predilection locations for development of most PPGLs (>95%) and therefore these locations should be the first to be scanned.

The diagnostic sensitivity and specificity of CT scanning is determined by the location of the tumor and by whether it is recurrent or metastatic disease. The sensitivity for adrenal tumors is >90% while that of extra-adrenal, recurrent or metastatic tumors is considerably lower. As CT scanning provides only information on the presence or absence of a mass, the specificity (75% to 80%) is substantially lower than sensitivity. Specific imaging characteristics such as density, contrast enhancement and contrast wash-out can improve the specificity, but CT still falls short to differentiate PPGLs from other adrenal tumors [33].

MRI imaging with or without gadolinium enhancement is in general the second best imaging modality but for extra-adrenal and skull base/neck paragangliomas MRI is preferred over CT scanning because better spatial resolution [34-36]. Nevertheless, several features that impair signal intensity such tumor necrosis or hemorrhage limits its diagnostic accuracy.

A second and complementary imaging step is functional imaging, which provides a substantially higher specificity than anatomical imaging and is particularly recommended for diagnosis of multi-focal or metastatic disease. For this modality specific ligands targeting either specific cell membrane transporters or vesicular catecholamine transport systems are available. Depending on the type of ligand single photon emission computed tomography (SPECT) is used, as is the case with iodine-123-metaiodobenzylguanidine (^{123}I-MIBG) and ^{111}In-pentetreotide. Other ligands such as ^{18}F-fluorodeoxyglucose (^{18}F-FDG), ^{18}F-fluorodihydroxyphenylalanine (^{18}F-FDOPA) and ^{68}Ga-labeled DOTA(0)-Tyr(3)-octreotide (^{68}Ga-DOTATATE) are used for photon emission tomography (PET), commonly combined with CT scanning [37].

The most frequently used ligand for PPGL localization is ^{123}I-MIBG for scintigraphy and SPECT. The sensitivity of ^{123}I-MIBG SPECT for detection of adrenal pheochromocytoma is excellent (nearly 100%), but is unacceptably low for extra-adrenal paragangliomas (56% to 75%) and metastases, particularly when associated with underlying succinate dehydrogenase (SDHx) mutations (<50%) [38-40]. Apart from this limitation, ^{123}I-MIBG is very useful to identify patients with metastatic PPGL because MIBG avid lesions indicate that these patients may benefit from treatment with therapeutic doses of ^{131}I-MIBG.

^{18}F-FDOPA PET imaging is recommended for both skull base and neck paragangliomas and for non-metastatic PPGLs [41]. The diagnostic performance of the newer ligands for PET imaging such as ^{18}F-FDG and ^{68}Ga-DOTATATE depends on specific clinical features, such as tumor location, metastases and underlying genetic mutation. Sensitivity of ^{18}F-FDG-PET is very high for metastatic disease, in particular in patients with SDHB-related metastatic PPGL [42]. ^{68}Ga-DOTATATE has a very high and selective affinity for tumor-associated somatostatin receptors type 2. Preliminary data show that it has an excellent diagnostic

accuracy in both sporadic and SDHB related metastatic PPGLs and the same applies to patients with skull base and neck paragangliomas [43-46].

The clinical impact of functional imaging in all PPGL patients remains undefended by required large prospective comparative clinical studies that take into account the aforementioned specific clinical features. In addition, solid data on specific ligands for functional imaging targeted to specific genotypes are limited except for SDHB related PPGLs. Yet, for the time being the choice of ligand should be personalized according to such features as recently suggested by the Endocrine Society guideline [15].

GENETIC TESTING

About 40% of all patients with a PPGL have a germline mutation in one of the 12 susceptibility genes and in 11% to 13% of all apparent sporadic cases a germline mutation can be detected [15,47-49]. The following genes are involved in hereditary PPGLs: neurofibromatosis type 1 (*NF1*), rearranged during transfection (*RET*), *VHL*, transmembrane domain protein 127 (*TMEM127*), MYC-associated factor X (*MAX*), fumarate hydratase (*FH*), malate dehydrogenase 2 (*MDH2*), and the succinate dehydrogenase A (*SDHA*), B (*SDHB*), C (*SDHC*), D (*SDHD*) and the succinate dehydrogenase complex assembly factor 2 (*SDHAF*). For most of the recently discovered tumor susceptibility genes penetrance has not yet been precisely established because of lack of long-term follow-up of non-index cases. However, the known penetrances vary from 2.5% in *NF1* to >90% in *SDHD* [50,51].

The genes most frequently mutated are *SDHB* and *VHL* while *MAX*, *TMEM127*, *MDH2*, *SDHAF2,* and *FH* are least frequently mutated. Mutations of *SDHB* gene are associated with an increased risk of development of metastatic disease (40% to 60%) [52-56] and mutation testing for this gene is particularly indicated in patients with extra-adrenal tumors (paragangliomas), particularly when large tumors or when producing 3-methoxytyramine.

Based on the pathogenic pathways from gene mutation to tumor development two cluster groups can be distinguished [21,57]. Cluster 1 tumors develop in patients with germline or somatic mutations in *VHL*, *SDHB*, *SDHD*, *SDHC*, *SDHAF2*, *SDHAF2*, hypoxia inducible factor 2α (*HIF2α*), prolyl hydroxylase 2 (*PHD2*), *MDH2*, *FH* genes and involve activation of hypoxia-angiogenic pathways. Cluster 2 tumors develop in patients with mutations in *RET*, *NF1*, *TMEM127*, and *MAX* and involve RAS and kinase signaling pathways. These pathogenic differences are associated with differences in biochemical phenotypes. Cluster 1 tumors are usually noradrenergic while cluster 2 tumors have an adrenergic phenotype except those with a *MAX* mutation, which are mixed adrenergic/noradrenergic. Tumors with SDHB and SDHD mutation may also produce additional 3-methoxytyramine. Therefore, among other factors than age and tumor location, the biochemical phenotype can guide the priority of the genes to be tested [15].

Genetic testing should at least be considered in all patients and is strongly indicated in specific patients such as those with a positive family history of PPGLs or carriers of tumor susceptibility gene mutations, and those with syndromic features or metastatic disease [15]. Other reasons to carry out mutation testing are the presence of risk factors for an underlying mutation: young patients, patients with multifocal or bilateral adrenal tumors, and patients with paragangliomas. Identification of a gene mutation in these patients might result in earlier detection of PPGLs and other neoplasms; thereby, reducing morbidity and improving survival. Genetic testing provides also an opportunity for a more personalized approach so that patient tailored management according to risk may result in timely detection of disease before metastases will develop. A typical example are the patients with *SDHB* mutations who carry a high risk for developing metastatic PPGLs. Early identification and close surveillance may be of long term benefit for such patient groups. Finally, it should be emphasized that genetic testing should be carried out in an accredited laboratory with the availability of pre- and posttest counseling.

PREOPERATIVE, SURGICAL, AND POSTSURGICAL MANAGEMENT

Proper presurgical preparation of PPGL patients by a multidisciplinary team is pivotal to guarantee the best possible outcome [58,59]. Both improved preoperative medical preparation and modern anesthesia and surgical techniques have resulted in a currently very low perioperative mortality of less than 1%. Medical preparation to prevent and minimize dangerous complications due to massive surges of released catecholamines from the tumor is still indispensible in all PPGL patients, including asymptomatic and normotensive patients [15,58,60]. This rational clinical practice is not evidence based as there are no randomised trials. There is however an abundance of case reports testifying on the potential catastrophic sequela if adequate preparation is omitted. More importantly, it should be

noted that there is no convincing evidence from randomized trials that it is really safe to abandon this longstanding practice.

An essential part of preoperative management is a cardiovascular evaluation, including an electrocardiogram and echocardiography. Patients with PPGL may have compromised cardiac function such as subclinical left ventricular failure [61]. Proper medical treatment of reduced left ventricular function may reduce the peroperative cardiovascular risks.

For achieving effective α-blockade, there is no compelling evidence so far that one of the two α-adrenoceptor antagonists, phenoxybenzamine or doxazosin, is preferred [62]. There is much more experience with the non-competitive α-adrenoceptor blocker phenoxybenzamine than with the competitive blocker doxazosin. Most centers take 10 to 14 days for this pharmacological pretreatment to achieve a stabile situation. A randomized trial to find out whether any of these drugs is preferred is under way. Calcium channel blockers have mainly been used as add-on drug to α-adrenoceptor blockade although some recent non-randomised studies found it also effective and safe as monotherapy [63,64]. A few centers still use the catecholamine-synthesis inhibitor α-methylparatyrosine (metyrosine) but there is no evidence that this drug, even as add-on drug, is really necessary for presurgical preparation. After installing α-adrenoceptor blockade, β-adrenoceptor blockade is part of the armentarium for tachycardia and tachyarrhythmias but should only be started after installment of proper α-adrenoceptor blockade [15].

Irrespective of the drug regimen, target sitting blood pressure is <130/80 mm Hg with avoiding upright systolic blood pressure of <90 mm Hg. Due to persistent vasodilation because of continued α-adrenoceptor blockade, there is a some risk of hypotension after tumor removal. To prevent this postsurgical hypotension, it is mandatory to prescribe a high-sodium diet and high fluid intake during the preparation period although this advice is not evidence-based [15]. The first 24 hours after tumor removal the patient should be strictly monitored to detect and treat hypertension, hypotension, or hypoglycemia [58]. In case of postsurgical hypotension, one important specific consideration is the possibility of adrenal insufficiency.

Minimal invasive laparoscopic tumor resection is the standard treatment with the posterior retroperitoneal approach as first choice in patients with pheochromocytoma [65]. The minimal invasive approach applies also to paragangliomas but this depends on location and tumor size. After minimal invasive tumor removal, patients experience less blood loss and have a shorter stay in hospital as compared to conventional open surgery. Partial adrenalectomy is the preferred option in patients with hereditary PPGLs (e.g., MEN2 and VHL syndromes) if technically possible [66]. It spares healthy adrenocortical tissue, thus avoiding lifelong steroid replacement therapy in most patients [66]. The underlying pathogenetic mutations in these syndromes drive however a certain risk of tumor recurrence in the remnant tissue after adrenal sparing surgery of 0% to 21% [66-68].

Follow-up of operated patients is essential for long term outcome for three reasons: surgery might be incomplete, tumors might recur or metastases may develop, even after many years. There are currently no validated reliable pathology criteria to predict that a primary tumor is benign, malignant or will evolve into metastatic disease in the future [69]. To ascertain that the tumor has been removed completely, measurement of plasma or urine metanephrines at 2 to 6 weeks after surgery is recommended. In case of persistently elevated biochemical test results, additional imaging studies are indicated [70]. Although the majority of patients is cured after successful surgery, there is a persistent risk of local or metastatic recurrences or a new tu-

Table 3. Key Points for Managing Pheochromocytoma/Paraganglioma

Low threshold of consideration of PPGL is key for early diagnosis
Search for clinical clues that require biochemical testing for PPGL
Consider syndromic features related to hereditary pheochromocytoma syndrome
Use as initial biochemical test: plasma or urinary metanephrines
Blood sampling: preferably after at least 20 minutes of supine rest
Consider proper pre-analytical test conditions, including use of interfering drugs
Check creatinine excretion for completeness of 24-hour urine sampling
Preferred assay method: use LC-MS/MS or HPLC-ED
Use as first imaging test: CT scan; MRI reserved for specific indications
Choice of functional imaging based on location and genetic background
Consider genetic testing in all patients in the framework of genetic counselling
Preoperative evaluation and medical preparation using α-adrenoceptor blockade are essential
Annual postsurgical follow-up for at least 10 years is mandatory for all patients
Follow-up should be lifelong in patients with an increased risk for recurrence

PPGL, pheochromocytoma or paraganglioma; LC-MS/MS, liquid chromatography with tandem mass spectrometry; HPLC-ED, high pressure liquid chromatography with electrochemical detection; CT, computed tomography; MRI, magnetic resonance imaging.

mor of 5% during 5 years follow-up [71] in patients with apparent complete resection of the tumor. Risk of recurrent disease is higher in young patients (<20 years), in those with syndromic presentations, in those with paragangliomas and in patients with large tumors. However, there is no 'safe' tumor size below which the risk is zero. A recent guideline recommended therefore to maintain postsurgical follow-up in all operated patients for at least 10 years. In patients at high-risk for recurrent disease such as the young ones, those who with a germline mutation, and those with an extra-adrenal or large tumor, follow-up should be continued lifelong [70]. Annual follow-up should include a medical history, proper blood pressure measurements and measurements of plasma or urinary fractionated metanephrines. The main recommendations for modern management of PPGLs are summarized in Table 3.

CONCLUSIONS

The last three decades have shown an enormous progress in the biochemical and functional diagnosis of PPGLs. In addition, the improved knowledge of the genetic background has not only contributed to a better understanding of the pathophysiological pathways involved but has also positively impacted clinical care. However, as a timely diagnosis and proper treatment can prevent potentially catastrophic complications, an early consideration of the presence of such tumor in patients is the key to provide the optimal outcome for patients and relatives.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Jacques W. M. Lenders *https://orcid.org/0000-0002-7658-4466*

REFERENCES

1. Lenders JW, Eisenhofer G. Pathophysiology and diagnosis of disorders of the adrenal medulla: focus on pheochromocytoma. Compr Physiol 2014;4:691-713.
2. Cawood TJ, Hunt PJ, O'Shea D, Cole D, Soule S. Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant: time for a rethink? Eur J Endocrinol 2009;161:513-27.
3. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR. The clinically inapparent adrenal mass: update in diagnosis and management. Endocr Rev 2004;25:309-40.
4. Whitelaw BC, Prague JK, Mustafa OG, Schulte KM, Hopkins PA, Gilbert JA, et al. Phaeochromocytoma [corrected] crisis. Clin Endocrinol (Oxf) 2014;80:13-22.
5. Stolk RF, Bakx C, Mulder J, Timmers HJ, Lenders JW. Is the excess cardiovascular morbidity in pheochromocytoma related to blood pressure or to catecholamines? J Clin Endocrinol Metab 2013;98:1100-6.
6. Riester A, Weismann D, Quinkler M, Lichtenauer UD, Sommerey S, Halbritter R, et al. Life-threatening events in patients with pheochromocytoma. Eur J Endocrinol 2015;173:757-64.
7. Prejbisz A, Lenders JW, Eisenhofer G, Januszewicz A. Cardiovascular manifestations of phaeochromocytoma. J Hypertens 2011;29:2049-60.
8. DeLellis RA, Lloyd R, Heitz P, Eng C. Pathology and genetics of tumours of endocrine organs. Lyon: International Agency for Research on Cancer Press; 2004.
9. Mills SE. Histology for pathologists. 4th ed. Philadelphia: Lippincott, Williams & Wilkins; 2012. Chapter 48, Paraganglia; p. 1277-99.
10. Williams MD, Tischler AS. Update from the 4th edition of the World Health Organization classification of head and neck tumours: paragangliomas. Head Neck Pathol 2017;11:88-95.
11. Eisenhofer G, Lenders JW, Goldstein DS, Mannelli M, Csako G, Walther MM, et al. Pheochromocytoma catecholamine phenotypes and prediction of tumor size and location by use of plasma free metanephrines. Clin Chem 2005;51:735-44.
12. Pamporaki C, Hamplova B, Peitzsch M, Prejbisz A, Beuschlein F, Timmers H, et al. Characteristics of pediatric vs adult pheochromocytomas and paragangliomas. J Clin Endocrinol Metab 2017;102:1122-32.
13. Manger WM. The protean manifestations of pheochromocytoma. Horm Metab Res 2009;41:658-63.
14. Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet 2005;366:665-75.
15. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2014;99:1915-42.

16. 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;90:2110-6.
17. Ayala-Ramirez M, Feng L, Johnson MM, Ejaz S, Habra MA, Rich T, 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;96:717-25.
18. Eisenhofer G, Rivers G, Rosas AL, Quezado Z, Manger WM, Pacak K. Adverse drug reactions in patients with phaeochromocytoma: incidence, prevention and management. Drug Saf 2007;30:1031-62.
19. Gimenez-Roqueplo AP, Dahia PL, Robledo M. An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. Horm Metab Res 2012;44:328-33.
20. Fishbein L. Pheochromocytoma and paraganglioma: genetics, diagnosis, and treatment. Hematol Oncol Clin North Am 2016;30:135-50.
21. Dahia PL. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer 2014;14:108-19.
22. Lenders JW, Pacak K, Walther MM, Linehan WM, Mannelli M, Friberg P, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287:1427-34.
23. Eisenhofer G, Peitzsch M. Laboratory evaluation of pheochromocytoma and paraganglioma. Clin Chem 2014;60:1486-99.
24. Timmers HJ, Pacak K, Huynh TT, Abu-Asab M, Tsokos M, Merino MJ, et al. Biochemically silent abdominal paragangliomas in patients with mutations in the succinate dehydrogenase subunit B gene. J Clin Endocrinol Metab 2008;93:4826-32.
25. Eisenhofer G, Keiser H, Friberg P, Mezey E, Huynh TT, Hiremagalur B, et al. Plasma metanephrines are markers of pheochromocytoma produced by catechol-O-methyltransferase within tumors. J Clin Endocrinol Metab 1998;83:2175-85.
26. de Jong WH, Eisenhofer G, Post WJ, Muskiet FA, de Vries EG, Kema IP. Dietary influences on plasma and urinary metanephrines: implications for diagnosis of catecholamine-producing tumors. J Clin Endocrinol Metab 2009;94:2841-9.
27. Willemsen JJ, Sweep CG, Lenders JW, Ross HA. Stability of plasma free metanephrines during collection and storage as assessed by an optimized HPLC method with electrochemical detection. Clin Chem 2003;49:1951-3.
28. Willemsen JJ, Ross HA, Lenders JW, Sweep FC. Stability of urinary fractionated metanephrines and catecholamines during collection, shipment, and storage of samples. Clin Chem 2007;53:268-72.
29. Darr R, Kuhn M, Bode C, Bornstein SR, Pacak K, Lenders JW, et al. Accuracy of recommended sampling and assay methods for the determination of plasma-free and urinary fractionated metanephrines in the diagnosis of pheochromocytoma and paraganglioma: a systematic review. Endocrine 2017;56:495-503.
30. Amar L, Eisenhofer G. Diagnosing phaeochromocytoma/paraganglioma in a patient presenting with critical illness: biochemistry versus imaging. Clin Endocrinol (Oxf) 2015;83:298-302.
31. Yu R, Nissen NN, Chopra P, Dhall D, Phillips E, Wei M. Diagnosis and treatment of pheochromocytoma in an academic hospital from 1997 to 2007. Am J Med 2009;122:85-95.
32. Eisenhofer G, Goldstein DS, Walther MM, Friberg P, Lenders JW, Keiser HR, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. J Clin Endocrinol Metab 2003;88:2656-66.
33. Leung K, Stamm M, Raja A, Low G. Pheochromocytoma: the range of appearances on ultrasound, CT, MRI, and functional imaging. AJR Am J Roentgenol 2013;200:370-8.
34. Ilias I, Sahdev A, Reznek RH, Grossman AB, Pacak K. The optimal imaging of adrenal tumours: a comparison of different methods. Endocr Relat Cancer 2007;14:587-99.
35. Jalil ND, Pattou FN, Combemale F, Chapuis Y, Henry JF, Peix JL, et al. Effectiveness and limits of preoperative imaging studies for the localisation of pheochromocytomas and paragangliomas: a review of 282 cases. French Association of Surgery (AFC), and The French Association of Endocrine Surgeons (AFCE). Eur J Surg 1998;164:23-8.
36. Gimenez-Roqueplo AP, Caumont-Prim A, Houzard C, Hignette C, Hernigou A, Halimi P, et al. Imaging work-up for screening of paraganglioma and pheochromocytoma in SDHx mutation carriers: a multicenter prospective study from the PGL.EVA Investigators. J Clin Endocrinol Metab 2013;98:E162-73.
37. Taieb D, Timmers HJ, Hindie E, Guillet BA, Neumann HP, Walz MK, et al. EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J

Nucl Med Mol Imaging 2012;39:1977-95.
38. Fiebrich HB, Brouwers AH, Kerstens MN, Pijl ME, Kema IP, de Jong JR, 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;94:3922-30.
39. Wiseman GA, Pacak K, O'Dorisio MS, Neumann DR, Waxman AD, Mankoff DA, et al. Usefulness of 123I-MIBG scintigraphy in the evaluation of patients with known or suspected primary or metastatic pheochromocytoma or paraganglioma: results from a prospective multicenter trial. J Nucl Med 2009;50:1448-54.
40. Timmers HJ, Chen CC, Carrasquillo JA, Whatley M, Ling A, Eisenhofer G, et al. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. J Natl Cancer Inst 2012;104:700-8.
41. Timmers HJ, Taieb D, Pacak K. Current and future anatomical and functional imaging approaches to pheochromocytoma and paraganglioma. Horm Metab Res 2012;44:367-72.
42. Timmers HJ, Kozupa A, Chen CC, Carrasquillo JA, Ling A, Eisenhofer G, et al. 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;25:2262-9.
43. Janssen I, Blanchet EM, Adams K, Chen CC, Millo CM, Herscovitch P, et al. Superiority of [68Ga]-DOTATATE PET/CT to other functional imaging modalities in the localization of SDHB-associated metastatic pheochromocytoma and paraganglioma. Clin Cancer Res 2015;21:3888-95.
44. Janssen I, Chen CC, Millo CM, Ling A, Taieb D, Lin FI, 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;43:1784-91.
45. Maurice JB, Troke R, Win Z, Ramachandran R, Al-Nahhas A, Naji M, 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;39:1266-70.
46. Janssen I, Chen CC, Taieb D, Patronas NJ, Millo CM, Adams KT, 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;57:186-91.
47. Flynn A, Benn D, Clifton-Bligh R, Robinson B, Trainer AH, James P, et al. The genomic landscape of phaeochromocytoma. J Pathol 2015;236:78-89.
48. Pillai S, Gopalan V, Smith RA, Lam AK. Updates on the genetics and the clinical impacts on phaeochromocytoma and paraganglioma in the new era. Crit Rev Oncol Hematol 2016;100:190-208.
49. Brito JP, Asi N, Bancos I, Gionfriddo MR, Zeballos-Palacios CL, Leppin AL, et al. Testing for germline mutations in sporadic pheochromocytoma/paraganglioma: a systematic review. Clin Endocrinol (Oxf) 2015;82:338-45.
50. Walther MM, Herring J, Enquist E, Keiser HR, Linehan WM. Von Recklinghausen's disease and pheochromocytomas. J Urol 1999;162:1582-6.
51. Ricketts CJ, Forman JR, Rattenberry E, Bradshaw N, Lalloo F, Izatt L, et al. Tumor risks and genotype-phenotype-proteotype analysis in 358 patients with germline mutations in SDHB and SDHD. Hum Mutat 2010;31:41-51.
52. Neumann HP, Pawlu C, Peczkowska M, Bausch B, McWhinney SR, Muresan M, et al. Distinct clinical features of paraganglioma syndromes associated with SDHB and SDHD gene mutations. JAMA 2004;292:943-51.
53. Amar L, Bertherat J, Baudin E, Ajzenberg C, Bressac-de Paillerets B, Chabre O, et al. Genetic testing in pheochromocytoma or functional paraganglioma. J Clin Oncol 2005;23:8812-8.
54. King KS, Prodanov T, Kantorovich V, Fojo T, Hewitt JK, Zacharin M, et al. Metastatic pheochromocytoma/paraganglioma related to primary tumor development in childhood or adolescence: significant link to SDHB mutations. J Clin Oncol 2011;29:4137-42.
55. Burnichon N, Rohmer V, Amar L, Herman P, Leboulleux S, Darrouzet V, et al. The succinate dehydrogenase genetic testing in a large prospective series of patients with paragangliomas. J Clin Endocrinol Metab 2009;94:2817-27.
56. Gimenez-Roqueplo AP, Favier J, Rustin P, Rieubland C, Crespin M, Nau V, et al. Mutations in the SDHB gene are associated with extra-adrenal and/or malignant phaeochromocytomas. Cancer Res 2003;63:5615-21.
57. Burnichon N, Buffet A, Gimenez-Roqueplo AP. Pheochromocytoma and paraganglioma: molecular testing and personalized medicine. Curr Opin Oncol 2016;28:5-10.

58. Naranjo J, Dodd S, Martin YN. Perioperative management of pheochromocytoma. J Cardiothorac Vasc Anesth 2017 Feb 4 [Epub]. https://doi.org/10.1053/j.jvca.2017.02.023.
59. Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab 2007;92:4069-79.
60. Agarwal A, Gupta S, Mishra AK, Singh N, Mishra SK. Normotensive pheochromocytoma: institutional experience. World J Surg 2005;29:1185-8.
61. Agarwal G, Sadacharan D, Kapoor A, Batra A, Dabadghao P, Chand G, et al. Cardiovascular dysfunction and catecholamine cardiomyopathy in pheochromocytoma patients and their reversal following surgical cure: results of a prospective case-control study. Surgery 2011;150:1202-11.
62. van der Zee PA, de Boer A. Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. Neth J Med 2014;72:190-201.
63. Siddiqi HK, Yang HY, Laird AM, Fox AC, Doherty GM, Miller BS, et al. Utility of oral nicardipine and magnesium sulfate infusion during preparation and resection of pheochromocytomas. Surgery 2012;152:1027-36.
64. Brunaud L, Boutami M, Nguyen-Thi PL, Finnerty B, Germain A, Weryha G, et al. Both preoperative alpha and calcium channel blockade impact intraoperative hemodynamic stability similarly in the management of pheochromocytoma. Surgery 2014;156:1410-7.
65. Barczynski M, Konturek A, Nowak W. Randomized clinical trial of posterior retroperitoneoscopic adrenalectomy versus lateral transperitoneal laparoscopic adrenalectomy with a 5-year follow-up. Ann Surg 2014;260:740-7.
66. Castinetti F, Taieb D, Henry JF, Walz M, Guerin C, Brue T, et al. Management of endocrine disease: outcome of adrenal sparing surgery in heritable pheochromocytoma. Eur J Endocrinol 2016;174:R9-18.
67. Castinetti F, Qi XP, Walz MK, Maia AL, Sanso G, Peczkowska M, et al. Outcomes of adrenal-sparing surgery or total adrenalectomy in phaeochromocytoma associated with multiple endocrine neoplasia type 2: an international retrospective population-based study. Lancet Oncol 2014;15:648-55.
68. 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 follow up. J Urol 2010;184:1855-9.
69. Tischler AS, deKrijger RR. 15 Years of paraganglioma: pathology of pheochromocytoma and paraganglioma. Endocr Relat Cancer 2015;22:T123-33.
70. Plouin PF, Amar L, Dekkers OM, Fassnacht M, Gimenez-Roqueplo AP, Lenders JW, et al. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. Eur J Endocrinol 2016;174:G1-10.
71. Amar L, Lussey-Lepoutre C, Lenders JW, Djadi-Prat J, Plouin PF, Steichen O. Management of endocrine disease: recurrence or new tumors after complete resection of pheochromocytomas and paragangliomas: a systematic review and meta-analysis. Eur J Endocrinol 2016;175:R135-45.