



Update on Modern Management of Pheochromocytoma and Paraganglioma

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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 ⁶⁸Ga-DOTATATE (⁶⁸Ga-labeled DOTA(0)-Tyr(3)-octreotide) will probably replace ¹²³I-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 cata-

strophic 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 have a parasympathetic origin [9,10]. In terms of biochemical pheno-

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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 de-

hydrogenase B (SDHB) mutations, large tumor size, dopaminergic phenotype, multifocal tumors, and extra-adrenal location [16,17].

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

Table 1. Indications for Biochemical Testing for Pheochromocytoma/Paraganglioma

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| 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].

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 proceeding 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 (¹²³I-MIBG) and ¹¹¹In-pentetreotide. Other ligands such as ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG), ¹⁸F-fluorodihydroxyphenylalanine (¹⁸F-FDOPA) and ⁶⁸Ga-labeled DOTA(0)-Tyr(3)-octreotide (⁶⁸Ga-DOTATATE) are used for photon emission tomography (PET), commonly combined with CT scanning [37].

The most frequently used ligand for PPGL localization is ¹²³I-MIBG for scintigraphy and SPECT. The sensitivity of ¹²³I-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, ¹²³I-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 ¹³¹I-MIBG.

¹⁸F-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 ¹⁸F-FDG and ⁶⁸Ga-DOTATATE depends on specific clinical features, such as tumor location, metastases and underlying genetic mutation. Sensitivity of ¹⁸F-FDG-PET is very high for metastatic disease, in particular in patients with SDHB-related metastatic PPGL [42]. ⁶⁸Ga-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 2 α (*HIF2 α*), 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 indispensable 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 perioperative 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 stable 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 armamentarium for tachycardia and tachyarrhythmias but should only be started after installation 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 hered-

itary 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

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| 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.

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