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Pheochromocytoma as a catecholamine producing tumor: Implications for clinical practice

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Abstract

Pheochromocytomas are catecholamine-producing tumors presenting with various clinical symptoms, but mostly with headache, sweating, palpitations and hypertension. If not properly diagnosed, secretion of catecholamines may lead to fatal cardiovascular consequences. Biochemical testing for pheochromocytoma should be performed not only in symptomatic subjects or in subjects with adrenal incidentaloma but also in subjects with a genetic predisposition for pheochromocytoma (multiple endocrine neoplasia type 2, Von Hippel–Lindau (VHL) syndrome, neurofibromatosis type 1 (NF 1) and mutations of succinate dehydrogenase (SDH) genes). Once a pheochromocytoma is proven, computed tomography (CT), magnetic resonance imaging (MRI) and functional imaging with [¹²³I]-MIBG may be used for tumor localization. Adequate medical pre-treatment is essential for successful operation which is performed in most cases by laparoscopy. After tumor removal, further follow-up is necessary due to possible recurrence. Although prognosis after tumor resection is excellent, a significant proportion of pheochromocytomas recur, some as metastases. Thus, appropriate follow-up is mandatory.

Keywords: *Adrenoceptor antagonists, catecholamines, dopamine, epinephrine, genetic testing, laparoscopic surgery*

Pheochromocytomas are tumors arising from chromaffin cells of the adrenal medulla that synthesize, store, metabolize and usually but not always secrete catecholamines. Paragangliomas are tumors arising from extra-adrenal chromaffin cells and can originate either from sympathetic nervous system associated chromaffin tissue (mainly abdomen and pelvis, less frequently thorax) or parasympathetic associated chromaffin tissue (head and neck). Sympathetic paragangliomas are usually hormonally active and are sometimes called extra-adrenal pheochromocytomas. They occur less frequently than adrenal pheochromocytomas (Lenders et al. 2005).

Pheochromocytoma is a rare cause of secondary hypertension, with a prevalence of about 0.2–0.6% (Ariton et al. 2000; Omura et al. 2004). This contrasts

with primary aldosteronism, which has a prevalence among unselected populations of hypertensives of 5–10% (Gordon et al. 1994; Rossi et al. 2006).

In contrast to the low prevalence of pheochromocytoma in hypertension, diagnosis of pheochromocytoma should always be ruled out in subjects with incidentally discovered adrenal tumors, since in this clinical condition the prevalence of pheochromocytoma may reach 4–5% (Mannelli et al. 1999; Mantero et al. 2000; Kasperlik-Zaluska et al. 2006). The prevalence of adrenal incidentalomas increases with age and may reach 7% in subjects more than 70 years old (Grumbach et al. 2003).

The prevalence of pheochromocytoma in autopsy studies (~0.05%) also indicates that many tumors are missed, resulting in premature mortality (McNeil et al.

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2000; Khorram-Manesh et al. 2006). Unlike other cancers, the typical age for diagnosis of sporadic pheochromocytoma is middle age. Pheochromocytomas with genetic syndromes are diagnosed earlier (Bravo and Tagle 2003). When diagnosed in children, pheochromocytoma often presents with extra-adrenal and multifocal involvement (Barontini et al. 2006).

Clinical presentation

The clinical presentation of pheochromocytoma is highly variable. Diagnosis may therefore be delayed. The vast majority of symptoms and signs are attributable to the excess of catecholamines which may be released by tumors continuously or paroxysmally. Clinical presentation may also depend on desensitization of catecholamine receptors as demonstrated in a study using a rat model of pheochromocytoma (Tsujiimoto et al. 1987). Sulfoconjugation of adrenal catecholamines is the other mechanism by which the action of catecholamines is modulated (Kuchel et al. 1986). This may lead to lack of correlation between levels of released catecholamines and clinical symptoms, even during spells (Bravo and Tagle 2003).

The most common signs of catecholamine excess are hypertension, palpitations and tachycardia, headache, pallor, sweating and feelings of panic or anxiety. Less common signs are nausea, flushing, fever and constipation.

Headache, palpitations and sweating constitute a typical triad for pheochromocytoma and together with hypertension should always arouse suspicion of pheochromocytoma. The metabolic action of catecholamines may lead to weight loss, disturbances in glucose metabolism, including diabetes mellitus or lactic acidosis. Co-incidence of hypertension and diabetes mellitus type 2 in lean young or middle aged subjects is also suspicious for pheochromocytoma (Batide-Alanore et al. 2003). The frequency of clinical symptoms and signs is lower in hereditary forms of pheochromocytoma (Table I), presumably due to active screening (Pacak et al. 2005). Subjects with initial presentation of pheochromocytoma as incidentaloma usually show mild symptoms and today

comprise up to 25% of all subjects with diagnosed pheochromocytoma (Amar et al. 2005b).

Paroxysmal signs and symptoms, a consequence of episodic secretion of catecholamines, provide compelling clues for a pheochromocytoma. Surgical anesthesia and tumor manipulation are the most well known stimuli to elicit a catecholaminergic crisis. Food, micturition (urinary bladder pheochromocytoma) and various chemical compounds or drugs (e.g. glucagon, histamine, radiographic contrast agents, tyramine, metoclopramide, tricyclic antidepressants and β -blockers) may also elicit paroxysms (Lenders et al. 2005). Spells are usually unpredictable with various intervals, but for individual patients stereotypic in nature, usually lasting from anything between several minutes and 1 h. However, the most typical complaints such as headache, palpitations and sweating are nonspecific and often result in delay of diagnosis.

Hypertension in pheochromocytoma occurs in up to 80–90% of patients with tumors detected because of signs and symptoms. High blood pressure may present in sustained or paroxysmal forms, the latter either on a background of normotension or hypertension (Kaplan 2006). In up to 10–20% of subjects with pheochromocytoma, orthostatic hypotension may occur in those with sustained hypertension (Streeten and Anderson 1996). Contrasting with other forms of secondary hypertension where only one circulating hormone is responsible for the development of hypertension, pheochromocytoma may be characterized by the overproduction of three circulating catecholamines—norepinephrine, epinephrine and in a minority of cases, dopamine. The catecholamines exhibit different effects on different catecholamine receptors—typically norepinephrine-mediated stimulation of α -receptors leads to vasoconstriction whereas epinephrine also stimulates β_2 -receptors, causing vasodilatation. Subjects with predominantly norepinephrine-secreting pheochromocytoma (noradrenergic phenotype) develop hypertension more frequently than subjects with predominantly epinephrine-producing pheochromocytomas (adrenergic phenotype) who present more often with paroxysmal symptoms (Ito et al. 1992). Particularly adrenal pheochromocytomas often produce neuropeptide Y

Table I. Signs and symptoms in subjects with familial and sporadic pheochromocytoma.

Symptoms and signs	Multiple endocrine neoplasia 2 (<i>n</i> = 19, %)	Von Hippel–Lindau (<i>n</i> = 31, %)	Paraganglioma syndrome 4 (<i>SDHB</i>) (<i>n</i> = 33, %)	
			Sporadic (<i>n</i> = 37, %)	
Hypertension	42	19	73	> 90
Symptoms (overall)	53	32	88	> 90
Headache	32	26	57	92
Sweating	32	23	52	70
Palpitation	37	19	63	73
Anxiety	21	16	54	60

SDH, succinate dehydrogenase complex. Modified from Pacak et al. (2005) and Timmers et al. (2007).

and this compound potentiates norepinephrine-induced vasoconstriction (deS Senanayake et al. 1995). Dopamine-producing tumors are relatively rare and often present with normotension (Proye et al. 1986; Eisenhofer et al. 2005). Blood pressure in subjects with pheochromocytoma is prone to abrupt fluctuations (in some cases from hypotension to severe hypertension) (Pešek et al. 2005). Twenty four hour blood pressure monitoring in subjects with pheochromocytoma may often show an elevation rather than a decrease in nocturnal blood pressure compared to the daytime blood pressure and occurs more frequently even in comparison with other forms of endocrine hypertension such as primary aldosteronism or Cushing's syndrome (Zelinka et al. 2004). Prompt blood pressure changes in pheochromocytoma result in higher blood pressure variability during 24-h ambulatory blood pressure monitoring compared to subjects with essential hypertension, in particular during the daytime (Zelinka et al. 2005).

Other cardiovascular complications of pheochromocytoma include sudden death, arrhythmias (brady- and tachyarrhythmias), myocardial infarction without preexisting coronary atherosclerosis, heart failure due to toxic catecholamine cardiomyopathy, dissecting aortic aneurysm, hypertensive encephalopathy, cerebrovascular accidents and noncardiogenic pulmonary edema or shock. Pheochromocytoma may also present with diabetic ketoacidosis, seizures, bowel pseudo-obstruction or multisystem crisis often with lactic acidosis (Brouwers et al. 2003). Other symptoms may be attributable to the co-secretion of other hormones or substances such as corticotropin-releasing hormone, adrenocorticotropin or interleukin six. Pheochromocytoma may also occur during pregnancy and thus may be misdiagnosed as pre-eclampsia. Accordingly, pheochromocytoma has been called the "Great Mimic" since its more than 80 manifestations can resemble so many other conditions that can confuse clinicians (Manger 2005).

Genetics of pheochromocytoma

To date, germ-line mutations in five different genes have been identified as causes of pheochromocytoma and functional paraganglioma (Table II). Hereditary pheochromocytoma is associated with multiple endocrine neoplasia type 2 (MEN 2A or MEN 2B), NF 1, VHL syndrome and familial functional paraganglioma and pheochromocytoma due to germ-line mutations of genes encoding SDH subunits B and D (*SDHB* and *SDHD*; Tables II and III). In general, the traits are inherited in an autosomal dominant pattern. Epidemiological studies among subjects with sporadic pheochromocytoma and functional paraganglioma have disclosed carriers of previously unrecognized germ-line mutations of four different genes (*VHL*, *RET*, *SDHB* and *SDHD*) in up to 24% of patients and

Table II. Main clinical features of syndromes associated with pheochromocytoma and functional paraganglioma.

<i>Von Hippel–Lindau</i>
Type 1 (<i>no pheochromocytomas</i>):
Renal cysts and carcinomas
Retinal and central nervous system hemangioblastomas
Pancreatic neoplasms and cysts
Endolymphatic sac tumors
Epididymal cystadenomas
Type 2 (<i>with pheochromocytomas</i>):
2A: Retinal and central nervous system hemangioblastomas
Endolymphatic sac tumors
Epididymal cystadenomas
Pheochromocytoma
2B: Renal cysts and carcinomas
Retinal and central nervous system hemangioblastomas
Pancreatic neoplasms and cysts
Endolymphatic sac tumors
Epididymal cystadenomas
Pheochromocytoma
2C: Pheochromocytoma only
<i>Multiple endocrine neoplasia 2</i>
2A: Medullary thyroid carcinoma
Pheochromocytoma
Hyperparathyroidism
Cutaneous lichen amyloidosis
2B: Medullary thyroid carcinoma
Pheochromocytoma
Multiple neuromas
Marfanoid habitus
FMTc: Familial medullary carcinoma only
<i>Neurofibromatosis 1</i>
Multiple fibromas on skin and mucosae
<i>Café au lait</i> skin spots
Pheochromocytoma
<i>Paraganglioma syndrome 1 (SDHD)</i>
Head and neck paragangliomas (carotid body tumors, vagal, jugular and tympanic paragangliomas)
Pheochromocytoma
Abdominal, pelvic and thoracic paragangliomas
<i>Paraganglioma syndrome 4 (SDHB)</i>
Abdominal, pelvic and thoracic paragangliomas
Pheochromocytoma
Head and neck paragangliomas

SDHB, succinate dehydrogenase subunit B gene; *SDHD*, succinate dehydrogenase subunit D gene.

thus challenging the traditional "rule of 10%" (Bornstein and Gimenez-Roqueplo 2006).

Patients with MEN 2-related pheochromocytoma often lack hypertension or other symptoms (occur only in about 40 and 50%, respectively; Table I). In most cases, medullary carcinoma of the thyroid is the first presentation of this syndrome. MEN 2-related pheochromocytomas are characterized by production of epinephrine and norepinephrine and are, therefore, best detected by elevations of plasma or urinary metanephrine, usually but not always in association with elevations of normetanephrine and parent catecholamines (Eisenhofer et al. 2001). MEN 2-related pheochromocytomas are almost always intra-adrenal, often bilateral (in 50–80%) and rarely malignant (<5%) (Pacak et al. 2005; Table III). In addition, as in most epinephrine-secreting pheochromocytomas,

Table III. Hereditary pheochromocytoma and paraganglioma: facts and figures.

Parameter	Von Hippel–Lindau	Multiple endocrine neoplasia 2	Neurofibromatosis 1	Paraganglioma syndrome 1 (<i>SDHD</i>)	Paraganglioma syndrome 4 (<i>SDHB</i>)
Gene	<i>VHL</i>	<i>RET</i>	<i>NF 1</i>	<i>SDHD</i>	<i>SDHB</i>
Chromosome	3p25–26	10q11.2	17q11.2	11q23	1p36.13
Protein	pVHL19 and pVHL30	Tyrosine-kinase receptor	Neurofibromin	Membrane-spanning subunit in the inner mitochondrial wall	Catalytic iron–sulfur protein
Frequency of germ-line mutations in an apparently sporadic pheochromocytoma/functional paraganglioma (%)	2–13	<5	3	0.5–7	3–10
Frequency of malignancy (%)	5	3	3–11	3	70
Tumor catecholamine phenotype*	NE	E	E	NE	NE, DA
Adrenal disease	++	++	++	+	+
Bilateral adrenal disease	++	++	+	+	–
Extra-adrenal disease	+	–	–	++	++
Multifocal disease	–	–	–	++	+

Adapted from Eisenhofer et al. (2004a); Lenders et al. (2005); Amar et al. (2005a); Bausch et al. (2006) and Timmers et al. (2007); *SDHB*, succinate dehydrogenase subunit B gene; *SDHD*, succinate dehydrogenase subunit D gene; ++, +, –, relative likelihoods of adrenal or extra-adrenal disease from high to low; * Tumor catecholamine phenotypes are designated as either predominantly epinephrine-producing (E) or predominantly norepinephrine-producing (NE) with possible dopamine (DA) co-secretion.

hypertension is more likely to be paroxysmal than sustained if present (Table I).

Overall about 20% of patients with *VHL* germ-line mutations develop pheochromocytoma (Ong et al. 2007). Unlike MEN 2, pheochromocytoma may be the first and also the sole presentation of *VHL* syndrome (type 2C of *VHL*—Table II). Pheochromocytomas in *VHL* syndrome have an exclusively noradrenergic phenotype, reflecting lack of production of epinephrine and thus present more with sustained than paroxysmal complaints (Eisenhofer et al. 2001). These tumors are often asymptomatic when diagnosed during regular screening in this syndrome (Table I). Biochemical diagnosis is best achieved from elevations of plasma or urinary normetanephrine (Eisenhofer et al. 2001). *VHL*-related tumors are mainly located intra-adrenally and occur in about 50% of patients bilaterally with a less than 5% incidence of metastases (Table III).

In NF 1, pheochromocytoma is relatively rare (<5%). Pheochromocytomas in NF 1 usually produce epinephrine and norepinephrine, may present with bilateral adrenal involvement and are also rarely malignant (Table III). Since genetic testing of the *NF 1* gene is not routinely performed, only one study has been published about prevalence of this disease among subjects with apparently sporadic pheochromocytoma (Bausch et al. 2006; Table III).

Mutations of *SDHB* and *SDHD* genes predispose their carriers to extra-adrenal (*SDHB* and *SDHD*) and multifocal disease (more frequently in *SDHD*)

(Neumann et al. 2004; Benn et al. 2006). Mutations of the *SDHD* gene are associated also with non-functional head and neck paragangliomas. Only head and neck paragangliomas have been described in *SDHC* mutations (Schiavi et al. 2005). Mitochondrial SDH functions in the Krebs cycle in the oxidation of succinate to fumarate. Since pheochromocytomas/paragangliomas appear to represent the sole clinical presentation of this syndrome, *SDH* mutations can often be diagnosed among subjects with apparently sporadic pheochromocytoma, particularly for those tumors with an extra-adrenal location (Table III). Carriers of *SDHB* mutations have a high risk of malignant disease (up to 70%; Table III; Gimenez-Roqueplo et al. 2003; Amar et al. 2005a; Benn et al. 2006; Brouwers et al. 2006). These tumors produce predominantly norepinephrine and *SDHB*-related malignant tumors also produce dopamine (Timmers et al. 2007). Subjects with *SDHB* mutation may present with more clinical symptoms and signs than subjects with other hereditary pheochromocytoma (MEN 2 and *VHL* syndromes; Table I).

Although *RET* gene acts as a proto-oncogene and the other remaining genes as tumor suppressor genes (*SDH* and *VHL* genes are involved in regulation of hypoxia-inducible genes), a unifying hypothesis about involvement of these genes in development of pheochromocytoma/paraganglioma has been proposed recently. All these genes induce apoptosis during normal development of neuronal precursor cells as nerve growth factor becomes limiting. Germ-line mutations of *NF 1*,

RET, *SDH* and *VHL* genes then allow sympathetic progenitors to escape from developmental apoptosis and so lead to their neoplastic transformation (Lee et al. 2005).

Should genetic testing be offered to all subjects with apparently sporadic pheochromocytoma? Although there are reasonable arguments for more widespread genetic testing, it is neither appropriate nor currently cost-effective to test every disease-causing gene in each patient with a pheochromocytoma or paraganglioma. Rather it seems to be more efficient to decide which genetic test should be performed according to the clinical presentation, including family history and physical examination (age at presentation, a single, bilateral, or extra-adrenal tumor or evidence of malignancy, and type of released catecholamine) as shown in Figure 1 and Table III (Bornstein and Gimenez-Roqueplo 2006; Gimenez-Roqueplo et al. 2006).

Biochemical testing

Tests with appropriately high sensitivity and specificity are needed for screening (Lenders et al. 2005). Catecholamines may be released by chromaffin cells only intermittently or at very low rates and thus can not serve as the method of choice to diagnose pheochromocytoma. In contrast, the metanephrines, *O*-methylated metabolites of catecholamines (norepinephrine to normetanephrine and epinephrine to metanephrine) are constantly produced within the chromaffin cells independently of catecholamine release (Eisenhofer et al. 2004). Measurements of fractionated metanephrines (i.e. normetanephrine and metanephrine measured separately) in plasma or in urine are now well established to prove superior diagnostic sensitivity and specificity over plasma or urinary catecholamines (Table IV; Lenders et al. 2002; Sawka et al. 2003; Grossman et al. 2006). Plasma metanephrines are most often measured in their free form as produced within tumors, whereas urinary metanephrines are commonly measured after a deconjugation step and largely represent sulfate-conjugates produced by an enzyme localized mainly

to gastrointestinal tissues (Eisenhofer et al. 2004b). This may explain higher diagnostic sensitivity of plasma metanephrines compared to urinary catecholamine metabolites (Lenders et al. 2002).

In certain cases, measurement of plasma dopamine or methoxytyramine may provide additional clinical and diagnostic information (Eisenhofer et al. 2005). Overproduction of dopamine may indicate malignant tumor potential (John et al. 1999).

As with all biochemical tests of catecholamine excess, a remaining problem is that a positive result for urinary or plasma metanephrines does not always reliably indicate a pheochromocytoma. To distinguish true positive from false positive results, it is advocated to take into account the extent of the elevation in biochemical test results (Grossman et al. 2006). While an elevation of plasma or urinary normetanephrine slightly above the upper reference intervals may only marginally increase the post-test probability of pheochromocytoma, an elevation of more than four-fold above those intervals is associated with close to 100% probability of the tumor (Eisenhofer et al. 2003). The actual level of the abnormal result should, therefore, be used to determine the need for immediate tumor localization studies vs. additional biochemical investigations. To accurately interpret results in the so called grey-zone, sample conditions should also be taken into consideration (e.g. medications, seated or recumbent position during venepuncture, patient's compliance during urine collection, associate clinical conditions). Additional help to distinguish true positive from false positive results may be afforded using the clonidine suppression test. Failure to suppress plasma norepinephrine (a decrease of <50% from basal or a persistent increased basal plasma norepinephrine of >3.00 nmol/l) after clonidine is highly predictive for pheochromocytoma (97%) (Bravo et al. 1981). In contrast, the negative predictive value of a normal test result is only 75%. If plasma normetanephrine is used (failure to suppress defined as a decrease of <40% from basal or a persistent increased basal plasma normetanephrine of >0.60 nmol/l) instead of plasma

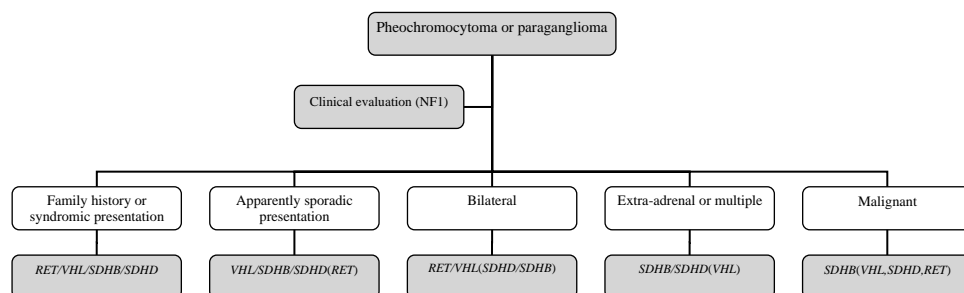


Figure 1. Algorithm for genetic testing for genes associated with pheochromocytoma or paraganglioma. Abbreviations: *RET*, rearranged during transfection; *SDHB*, succinate dehydrogenase subunit B gene; *SDHD*, succinate dehydrogenase subunit D gene; *VHL*, Von Hippel–Lindau gene; *NF 1*, neurofibromatosis 1. Genes in parenthesis: second choice testing. Adapted from Bornstein and Gimenez-Roqueplo (2006) and Gimenez-Roqueplo et al. (2006).

Table IV. Sensitivity and specificity of biochemical tests for diagnosis of pheochromocytoma.

Parameter	Sensitivity (%)	Specificity (%)
Plasma metanephrines	99	89
Plasma catecholamines	84	81
Urinary catecholamines	86	88
Urinary fractionated metanephrines	97	69
Urinary total metanephrines	77	93
Urinary vanillylmandelic acid (VMA)	64	95

Sensitivity values of all tests for familial pheochromocytoma are lower than for sporadic pheochromocytoma. The reverse is the case for the specificity values. Adapted from Lenders et al. (2002).

norepinephrine, the positive and negative predictive values of this test improve to 100 and 96%, respectively (Eisenhofer et al. 2003).

Imaging

Imaging studies for detecting pheochromocytoma are usually not indicated unless the biochemical diagnosis is strongly positive, primarily in subjects with suspected sporadic pheochromocytoma. However, in patients with a hereditary predisposition or a previous history of the tumor, where the pre-test probability of a tumor is higher, less-compelling biochemical evidence might justify imaging studies (Grossman et al. 2006).

Since the vast majority of suspected tumors arise from adrenals or chromaffin tissue in the abdomen, methods of choice are magnetic resonance imaging (MRI) or computed tomography (CT) of the entire abdomen including pelvis with and without contrast (Ilias and Pacak 2004). Advantages of CT compared to MRI are better availability, lower cost and shorter scanning time but MRI (T_2 -weighted sequences) is preferred in children, pregnant females and in subjects with allergy to contrast. MRI is also superior to CT for detecting extra-adrenal tumors (better sensitivity for small tumors), especially in chest and neck (Sahdev et al. 2005) and postoperatively because MRI unlike CT is not interfered with by artifacts caused by metal surgical clips. Both methods possess good sensitivity for detecting tumors but they do not provide sufficient specificity to differentiate pheochromocytoma from other possible pathologies, particularly in the adrenals.

To confirm the diagnosis of pheochromocytoma and to exclude multilocular or malignant involvement, functional imaging should be performed, in particular in tumors with higher potential of malignancy or multifocal involvement (epinephrine-secreting adrenal pheochromocytomas > 5 cm, all norepinephrine-secreting pheochromocytomas and functional paragangliomas) (Pacak et al. 2005).

Scintigraphy using preferentially [^{123}I]-metaiodobenzylguanidine [^{123}I]-MIBG) offers excellent specificity (95–100%) and good sensitivity (83–100%) for detecting adrenal tumors (Nielsen et al. 1996; van der Harst et al. 2001; Miskulin et al. 2003), but sensitivity for paragangliomas or malignant tumors (71 and 56%, respectively) is less than optimal (Erickson et al. 2001; Ilias et al. 2003).

For subjects with negative [^{123}I]-MIBG results, [^{111}In]-octreotide scanning or positron emission tomography with [^{18}F]-fluorodeoxyglucose may be useful (Shulkin et al. 1999; van der Harst et al. 2001). The latter modality is superior to [^{123}I]-MIBG for malignant and rapidly growing poorly-differentiated tumors. Other imaging agents for positron emission tomography include as [^{18}F]-fluorodopamine, [^{18}F]-fluorodopa, [^{11}C]-hydroxyephedrine, [^{18}F]-dihydroxyphenylalanine and [^{11}C]-epinephrine. All these imaging modalities are highly specific for pheochromocytoma (Grossman et al. 2006).

Management of pheochromocytoma

The correct clinical management of patients with pheochromocytoma relies on close collaboration between different specialists. In most patients, the tumor is cured by surgery. To minimize perioperative and postoperative morbidity and mortality, appropriate medical pretreatment is necessary at least 10–14 days before surgery. Most used drugs for medical pretreatment of pheochromocytoma are α - and β -adrenoceptor antagonists and calcium channel blockers (Prys-Robert 2000; van der Horst-Schrivers et al. 2006). Use of the non-competitive α -adrenoceptor antagonist phenoxybenzamine may offer the advantage over competitive α -adrenoceptor antagonists (e.g. doxazosine or prazosin) by avoiding any possibility of drug displacement from α -adrenoceptors by excessive increases in catecholamines during surgery. However, use of phenoxybenzamine must be counterbalanced with higher risk of postoperative hypotension (Bravo and Tagle 2003). Although the maximal tolerable doses of α -adrenoceptor antagonists are recommended for the surgical pretreatment, clinical evidence that this strategy results in improvement of cardiovascular stability during surgery is still lacking (Weismann et al. 2006). Use of β -blockers is indicated in subjects with tachycardia but only while on treatment with α -adrenoceptor antagonists. To avoid or to lessen the risk of orthostatic hypotension during treatment with α -adrenoceptor antagonists, salt and fluid intake should be increased. The additional advantage of this approach is that it reduces the risk of postoperative hypotension.

The surgical method of choice for pheochromocytoma removal is laparoscopy with transperitoneal or retroperitoneal approach (Walz et al. 2006). The choice of procedure depends mainly on surgical

experience and secondly on tumor dimensions (Wilhelm et al. 2006). In cases of bilateral or hereditary adrenal tumors, adrenal cortex-sparing surgery should be performed to minimize the risk of subsequent hypocortisolism. Advantages of laparoscopy over the conventional surgical approach are lower postoperative morbidity, and reduced hospital stay and expense. For treatment of hypertensive peaks and tachyarrhythmias during surgery, infusion of short acting drugs such as phentolamine, nicardipine, or sodium nitroprusside for blood pressure control and esmolol for tachycardias are used when necessary. Abrupt decrease of catecholamine levels after clamping off the venous drainage of the tumor to the general circulation is often accompanied by hypotension. Treatment requires fluid replacement and occasionally pressor agents (e.g. norepinephrine or phenylephrine) (Mannelli 2006). The other complication resulting from abrupt decrease of circulating catecholamines is hypoglycemia due to unopposed high insulin levels and low glycogen stores in liver (Kinney et al. 2002). This can be avoided by starting an IV infusion of 5% dextrose for 3–4 h immediately following tumor removal.

Currently, after proper medical preparation, operative mortality is less than 1% if performed by an experienced anesthesiologists and a skilful surgeon.

After the tumor removal, biochemical testing should be performed after about 14 days from surgery in order to check for remaining disease. If results of biochemical testing are entirely normal, resection is probably complete and those subjects with sporadic disease are likely cured. However, these patients should be followed-up for a risk of tumor recurrence or subsequent malignancy in at least annual intervals (Plouin et al. 1997). Those subjects at highest risk of subsequent malignancy (carriers of *SDHB* mutations, patients with functional paragangliomas and large adrenal tumors) and with hereditary pheochromocytomas require closer follow-up including clinical and biochemical assessment every 6–12 months (Mannelli 2006).

Malignant pheochromocytoma

Currently, the only criterion for malignancy is the presence of chromaffin cells at tissues sites where no chromaffin tissue should occur. To predict the potency of malignancy, several criteria and scoring systems have been developed on the basis of histopathology but perhaps the most predictive value are extra-adrenal tumor location, tumor size and presence of *SDHB* mutations. The prevalence of malignant pheochromocytoma is about 10% (5–26%); higher rates (up to 36%) have been reported in subjects with extra-adrenal tumors (O’Riordain et al. 1996; Ahlman 2006). The most frequent distant sites of metastatic involvement are bones (up to 70%), liver and lung. Those subjects with liver metastases may show shorter survival than those

with solitary bone metastases. Overall, the 5-year survival rate in malignant pheochromocytoma is about 50% (Lehnert et al. 2004).

Currently, there is no cure for malignant pheochromocytoma or paraganglioma. Surgical treatment may help to obtain tumor reduction and to control hypertension and other clinical signs and symptoms. However, there are no randomized trials demonstrating any survival advantage of tumor debulking, but reduced tumor volume may facilitate subsequent radio- or chemotherapy (Ahlman 2006). Subjects with lesions avid for [$^{121/131}\text{I}$]-MIBG scintigraphy may benefit from treatment with [^{131}I]-MIBG, particularly with high doses (Fitzgerald et al. 2006). Only a few subjects develop complete remission after chemotherapy (mostly cyclophosphamide, dacarbazine and vincristine) (Averbuch et al. 1988). In some cases, radiofrequency ablation or external beam radiation may be beneficial. Therapy with somatostatin analogs does not seem to offer any benefit (Lamarre-Cliche et al. 2002). To define the role of therapeutic doses of [^{177}Lu -DOTA 0]Octreotate in the treatment of metastatic paraganglioma, larger numbers of subjects treated with this radiopharmaceutical are needed (van Essen et al. 2006).

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