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Phaeochromocytoma and Paraganglioma

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Abstract

Phaeochromocytomas and paragangliomas are relatively uncommon tumours which may be manifest in many ways, specifically as sustained or paroxysmal hypertension, episodes of palpitations, sweating, headache and anxiety, or increasingly as an incidental finding. Recent studies have shown that an increasing number are due to germline mutations. This review concentrates on the diagnosis, biochemistry and treatment of these fascinating tumours.

Keywords

Phaeochromocytomas • Paragangliomas • Review • Diagnosis • Treatment • Malignant

1 Introduction

Phaeochromocytomas are uncommon tumours originating from the neural crest- derived chromafin cells in the adrenal medulla. They commonly produce one or more catecholamines: adrenaline (epinephrine), noradrenaline (norepinephrine) or dopamine, and the excess secretion of these causes a wide array of clinical features, including hypertension. The highest prevalence of phaeochromocytoma is seen in the fourth and fifth decades, with an equal incidence in men and women.

Although the annual incidence of phaeochromocytoma is predicted to be approximately 0.8 per 100,000 person years (Beard et al. 1983), this number might be an under-estimation, as autopsy studies have indicated that over 50 % of phaeochromocytomas found at autopsy were not clinically suspected (Sutton et al. 1981). Even though it is considered to be a rare cause of hypertension, accounting for only approximately 0.2 %, phaeochromocytomas should be diagnosed early as they cause significant morbidity with at least a 10 % possibility of malignancy

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and an even higher percentage of familial disease (Young 2011) (see below).

The great majority, some 95 %, of catecholamine-secreting tumours are in the abdomen, of which 90 % are intra-adrenal and 10 % are extra-adrenal and are referred to as paragangliomas (also known as extra-adrenal phaeochromocytomas). Approximately 10 % of catecholamine-secreting tumours are multiple (Bravo 1991).

2 Catecholamines and Their Receptors

Catecholamines exert many cardiovascular and metabolic effects including increasing heart rate, blood pressure, myocardial contractility and the velocity of cardiac conduction. Their action is via three main receptors: α, β, and dopaminergic. These receptors have several subtypes that have different physiological actions on the cardiovascular and central nervous systems (Table 1).

3 Clinical Presentation

The presentation of phaeochromocytomas can have a wide clinical spectrum from asymptomatic disease to non-specific symptoms leading all the way up to resistant hypertension and hypertensive crises. The clinical literature describes a classic clinical triad seen in phaeochromocytoma including headache, sweating and tachycardia. Although typical when present, this clinical triad is not commonly encountered in most patients with phaeochromocytomas.

Paroxysmal clinical features or 'spells' are a well-recognised consequence of episodic secretion and release of catecholamines. A spell can start with a sense of shortness of breath followed by palpitations and a throbbing headache. Peripheral vasoconstriction associated with such an episode leads to cold peripheries and facial pallor. Towards the end of the episode the patient may feel a sense of warmth and sweating. These can be either spontaneous or precipitated by postural change, medications (Table 2), exercise, or manoeuvres such as lifting and straining. The presentation of spells can be highly variable; however, they tend to be stereotypical for each patient. The frequency of episodes can vary as well, where some patients experience spells several times a day, while others only develop them very infrequently (Young 2011). It is important to bear in mind that these episodes are common and can be due to many other causes apart from

Table 1 Catecholamine receptors, their locations and main actions

Receptor		Location	Main action
α	α1	Postsynaptic receptor	Vascular and smooth muscle contraction causing vasoconstriction and increases in blood pressure
	α2	Presynaptic sympathetic nerve endings.	Inhibit release of noradrenaline causing suppression of central sympathetic outflow and decreased blood pressure
β	β1	Predominantly in cardiac tissue	Positive inotropic and chronotropic effects on the heart
			More responsive to isoproterenol (isoprenaline) than to adrenaline or noradrenaline
			Increase renin secretion
	β2	Bronchial, vascular smooth muscle	Bronchodilatation, vasodilatation in skeletal muscle
			Increase release of noradrenaline from sympathetic nerve terminals
	β3	Mainly in adipose tissue	Regulation of lipolysis and thermogenesis
D	D1	Cerebral, renal, mesenteric and coronary vessels	Local vasodilatation
	D2	Presynaptic sympathetic nerve endings in sympathetic ganglia and brain	Inhibit the release of noradrenaline, inhibits ganglionic transmission
			Inhibit prolactin release

Table 2 Commonly used medications that can precipitate hypertension/hypertensive crisis in phaeochromocytoma

Drugs	Example
Dopamine D2 receptor antagonists	Metoclopramide, sulpiride, chlorpromazine, prochlorperazine
β-Adrenergic receptor blockers	Propranolol, sotalol, timolol, nadolol, labetalol
Sympathomimetics	Ephedrine, fenfluramine, methylphenidate, phentermine
Opioid analgesics	Morphine, pethidine, tramadol
Noradrenaline reuptake inhibitors/tricyclic antidepressants	Amitriptyline, imipramine, including the newer SNRIs
Monoamine oxidase inhibitors	Tranylcypromine, moclobemide, phenelzine
Corticosteroids (rarely)	Dexamethasone, prednisone, hydrocortisone, betamethasone
Neuromuscular blocking agents	Succinylcholine, tubocurarine, atracurium

Table adapted from reference Lenders et al. (2014)

phaeochromocytoma. Facial flushing is described in many textbooks, but in our view is rarely seen. Concomitant swelling of the thyroid has been described (Nakamura et al. 2011).

Hypertension is one of the most common presenting features of catecholamine-secreting tumours. Several large retrospective case series have elaborated the prevalence of hypertension in patients with phaeochromocytomas to be between 51 % and 90 % (Baguet et al. 2004; Guerrero et al. 2009). The presentation of hypertension can be quite variable in phaeochromocytoma. It is usually stable and permanent; however, it can be paroxysmal with wide fluctuations, and resistant to treatment. Although uncommon, phaeochromocytoma can also present with postural symptoms with episodic *hypo*tension due to extreme blood pressure fluctuations. This has been reported in patients with predominantly adrenaline-producing tumors, where the presentation can be with hypotension or even shock (Streeten and Anderson 1996; Bergland 1989). Hypotension in these patients could be due to the catecholamine-induced intravascular volume depletion, an abrupt decline of catecholamine levels due to tumour necrosis, hypercalcaemia, desensitisation of adrenoceptors, or acute cardiovascular events such as acute myocardial infarction, tachyarrhythmia or aortic/coronary artery dissection.

Several case series have elaborated the association between phaeochromocytoma and hypertension. In one series, approximately 50 % of the patients were discovered due to hypertension of which half of these had hypertension that was paroxysmal in nature. The series further elaborates that, when the reason for the discovery of phaeochromocytoma was permanent hypertension, it was symptomatic, severe, and treatment resistant (Baguet et al. 2004). Moreover, approximately 10 % of patients in the series presented with normal blood pressure, which was commonly seen in patients with adrenal incidentalomas or in those undergoing screening for familial phaeochromocytoma. However, it is important to bear in mind that, in phaeochromocytoma, patients with normal blood pressure can still have life-threatening paroxysms of hypertension. There appears to be a more pathological effect on cardiac function than the hypertension *per se* would impose (Stolk et al. 2013).

Therefore, hypertension is the initial presentation in most patients with catecholamine excess, and one should be alerted to the possibility of a phaeochromocytoma in patients with hypertension, especially if the hypertension is:

- Paroxysmal, resistant or young onset (<20 years)
- Paradoxical despite therapy (especially during treatment with β-blockers)
- New onset or worsening of hypertension with tricyclic anti-depressants and other medications (Table 2)
- Severe symptomatic hypotension when initiating therapy with α-blockers

Table 3 Frequency of common signs and symptoms in phaeochromocytoma

Symptom		Frequency (%)
Hypertension	Sustained	50
	Paroxysmal	30
	Orthostatic	12
Headache		60–90
Palpitations		50–70
Sweating		55–75
Pallor		40
Weight loss		20–40
Fatigue		25–40
Anxiety and panic		20–40
Hyperglycaemia		40
Fever		60

Table adapted from reference Young (2011) and Lenders et al. (2005)

- Severe hypertension or hypertensive crises following any procedure (eg. anaesthesia, surgery, or angiography)
- In pregnant patients with hypertension not typical of pregnancy-induced hypertension

With the widespread availability of imaging techniques, the detection of adrenal incidentalomas has increased over the last few decades. Approximately 5 % of all incidentally-detected adrenal tumours are found to be phaeochromocytomas, and some 25 % of all phaeochromocytomas are now being incidentally discovered during imaging studies for unrelated disorders (Young 2011; Lenders et al. 2005; Mantero et al. 2000).

Apart from hypertension and incidental discovery, phaeochromocytoma can present with a wide variety of clinical features (Table 3).

Cardiovascular complications are another well-recognised presentation in phaeochromocytoma. Apart from the cardiac emergencies such as myocardial infarction, cardiac arrhythmias and aneurysms, it can present with more long-standing cardiac complications such as dilated or hypertrophic cardiomyopathy and congestive heart failure (Liao et al. 2000).

Excess catecholamines can also affect the gastrointestinal system including inhibition of peristalsis causing constipation or even pseudo-obstruction or ileus. Moreover, vasoconstriction of the mesenteric artery can lead to ischaemic enterocolitis and intestinal necrosis.

In the clinical evaluation of patients with phaeochromocytoma, it is important to always bear in mind the syndromic nature of phaeochromocytoma, and to actively seek out features such as Marfanoid body habitus, *café-au-lait* spots, axillary freckling, subcutaneous neurofibromas, mucosal neuromas on the tongue, retinal angiomas, iris hamartomas and multiple other clinical features suggestive of an underlying clinical syndrome.

In summary, patients with excess catecholamines can show a wide spectrum of clinical features and it is recommended that one considers the possibility of a phaeochromocytoma especially when patients exhibit certain clinical features (Lenders et al. 2014):

- Hyperadrenergic spells (episodic self-limiting non-exertional palpitations, diaphoresis, headache, pallor)
- A personal or family history of familial syndrome that predisposes to catecholamine-secreting tumors (e.g., MEN2, NF1, VHL, etc.)
- An adrenal incidentaloma
- Idiopathic dilated cardiomyopathy

4 Familial Phaeochromocytoma

In contrast to the conventional teaching of a 10 % familial tendency, recent studies have identified multiple genes in association with phaeochromocytoma, with up to 30 % or possibly more exhibiting a disease-causing germ-line mutation. Along with the well-recognised genetic disorders such as multiple endocrine neoplasia-2 (MEN-2), neurofibromatosis type 1 and Von-Hippel Lindau syndrome, nearly 21 genes have been identified in association with phaeochromocytoma. Most phaeochromocytomas due to syndromic causes present at a younger age than their sporadic counterparts, although part of this earlier identification my relate to genetic or biochemical screening.

Multiple endocrine neoplasia-2 is the one of the earliest syndromes to have been associated with phaeochromocytoma. Interestingly, only half of the patients with phaeochromocytoma with MEN2 exhibit clinical feature and fewer patients have hypertension (Pomares et al. 1998). This might relate to early diagnosis due to other syndromic associations or screening. MEN 2A (now known as MEN2) is characterised by medullary thyroid cancer in all patients, phaeochromocytoma in 40–50 % and primary hyperparathyroidism in 20 %. MEN2B (now known as MEN3) accounts for approximately 5 % of MEN syndromes and has a similar percentage of medullary carcinoma and phaeochromocytoma along with mucocutaneous neuromas; however, it is not associated with hyperparathyroidism. The genetic defect in MEN2 and MEN3 is in the *RET* proto-oncogene on chromosome 10, which is inherited in an autosomal dominant pattern with high penetrance. Several codon mutations in the RET gene have been associated with MEN2/3 and these are gain-of-function mutations: the great majority of MEN2 are associated with a mutation at codon 634 which codes for the extra-cellular domain of RET, while for MEN3 the dominant mutation at 918 codes for part of the intra-cellular domain. It has been hypothesised that the subtle changes in the clinical presentation is due to these genetic variations in the mutation (Mulligan and Ponder 1995). It is vital to identify phaeochromocytomas in these patients to avoid perioperative hypertensive crisis during thyroidectomy for medullary thyroid carcinoma. Phaeochromocytomas seen in MEN2 are frequently bilateral and almost invariably benign.

Neurofibromatosis type 1 (NF1) is another autosomal dominant disorder, characterized by neurofibromas, *café-au-lait* spots, freckling, Lisch nodules, phaeochromocytoma and paraganglioma: 2 % of patients with the NF1 gene present with solitary and benign pheochromocytoma. However, they can occasionally be bilateral or extra-adrenal (Walther et al. 1999). Insulinomas and somatostatinomas are also seen in this syndrome.

In von Hippel-Lindau (VHL) syndrome, phaeochromocytomas are more frequently bilateral with mediastinal, abdominal or pelvic paragangliomas. Other syndromic features of VHL include CNS hemangioblastoma, retinal angioma, clear cell renal cell carcinoma, pancreatic neuroendocrine tumours and middle ear tumours. As in MEN-2, VHL too has considerable genetic variability among kindreds with certain mutations causing a higher frequency (up to 20 %) of phaeochromocytoma, (Dluhy 2002). Interestingly, patients habouring the VHL mutation have a lower incidence of hypertension and have elevated normetanephrine, in contrast to patients with MEN-2, who show elevated metanephrine levels (Eisenhofer et al. 2001). Malignancy is rare but does occur.

Another important cause for familial catecholamine-hypersecreting tumours is succinate dehydrogenase (SDH) gene mutation. Several mutations in the SDH gene have been identified including SDHB, SDHC, SDHD, SDHAF2, and (very rarely) SDHA. Similar to the previously mentioned mutations, SDH mutations are also inherited in an autosomal dominant pattern. However, interestingly, SDHD and SDHAF2 have a paternal inheritance pattern due to maternal imprinting. In patients with SDH mutations causing paragangliomas/phaeochromocytomas, the type of catecholamine produced depends on its location. An SDH-induced paraganglioma is different from phaeochromocytoma in general in the fact that tissue expression of PMNT in these tumors is minimal, which means that the preferential catecholamine production is norepinephrine or dopamine and they produce normetanephrine, or normetanephrine and methoxytyramine, or rarely only methoxytyramine (Timmers et al. 2007). Interestingly, tumours only producing methoxytyramine are usually SDH tumors. Of abdominal paragangliomas, most secrete noradrenaline, often both noradrenaline and dopamine and rarely only dopamine. The rate of noradrenaline production is much lower in head-and-neck paragangliomas. Most mutations in the SDHD, SDHAF2 and SDHC are associated with non-catecholamine secreting, head-and-neck paragangliomas (Kantorovich et al. 2010). Although SDHB mutation commonly presents

with extra-adrenal abdominal or thoracic disease, a primary presentation with an adrenal phaeochromocytoma is still evident in some patients. Approximately 1/3 of patients with SDHB mutations present with multifocal disease (Kantorovich et al. 2010). Moreover, carriers of SDHB mutations can develop early onset abdominal, pelvic, and thoracic catecholamine-secreting paragangliomas that are more likely to be malignant, possibly in up to 50 % of patients. SDHB carriers who develop malignant paragangliomas are more likely to develop other neoplasms including papillary thyroid tumours, renal cell carcinoma, neuroblastoma, or gastrointestinal stromal tumours (GIST) (Neumann et al. 2004). A link has also been shown between SDH mutation status and pituitary tumours (Galan and Kann 2013).

Apart from these more commonly known mutations, several new mutations have been identified in association with pheochromocytoma. TMEM127 is a recently identified germline mutation, inherited autosomal dominantly, commonly associated with benign unilateral adrenal phaeochromocytoma. However, there are few case studies of bilateral, malignant and extra-adrenal disease. Interestingly, the presentation of these patients is in the fifth decade, more in keeping with the onset of sporadic phaeochromocytoma rather than the familial form.

The *MAX* (Myc-associated factor X) gene is another more recently reported susceptibility gene, which is inherited as autosomal dominant and, similar to SDHD and SDHAF2, has a paternal inheritance pattern. The majority of patients with MAX mutations present at a younger age and tend to have bilateral or unilateral phaeochromocytoma with an increased potential to develop malignant disease and predominantly produce noradrenaline (Dénes et al. 2015; Comino-Mendez et al. 2011).

Several other mutations such as HIF2α, KIF1β, fumarate hydratase and PHD2 have been reported recently, although detailed studies have yet to be performed on their syndromic associations and characteristics of phaeochromocytoma. (eg. Carney–Stratakis syndrome- familial paraganglioma and Gastrointestinal Stromal Tumours (GIST),). Finally, the recently-described Pacak-Zhuang syndrome, which shows an association between paragangliomas, polycythaemia and retinal angiomas with somatic mutation of HIF-2α, most likely occurs as a mosaicism similar to the McCune-Albright syndrome (Zhuang et al. 2012).

Genetic screening plays a vital role in the management of phaeochromocytoma, not only to detect other associated life-threatening conditions in the index patient but also for the diagnosis and treatment family members with certain mutations (eg, medullary carcinoma of the thyroid with *RET* mutations). Moreover, genetics can alert the physician to the malignant potential of phaeochromocytomas, especially in patients harbouring certain mutations (eg, SDHB), and to actively seek for the presence of metastases. Similar to the genetic mutation offering clues regarding character of the tumour, certain characteristics such as tumour location, the presence of metastases and the type of catecholamine synthesised can give clues to the possible causative mutation. Therefore, genetic analysis has become an important tool in the investigatory armamentarium for the evaluation and management of this rare syndrome. Accordingly, recently-published major guidelines recommend that all patients diagnosed with phaeochromocytoma/paraganglioma should be engaged in shared decision making for genetic testing for a possible somatic or germ line mutation (Lenders et al. 2014). Due to cost factors, the Endocrine Society recommends prioritising certain genetic screening based on the clinical and biochemical features (Fig. 1). Nevertheless, in Oxford we screen routinely for a panel of 10 genes in almost all patients. It has been shown that even in older patients with single benign phaeochromocytomas and no family history or syndromic featues, nearly 10 % will still harbour a germline mutation (Brito et al. 2015).

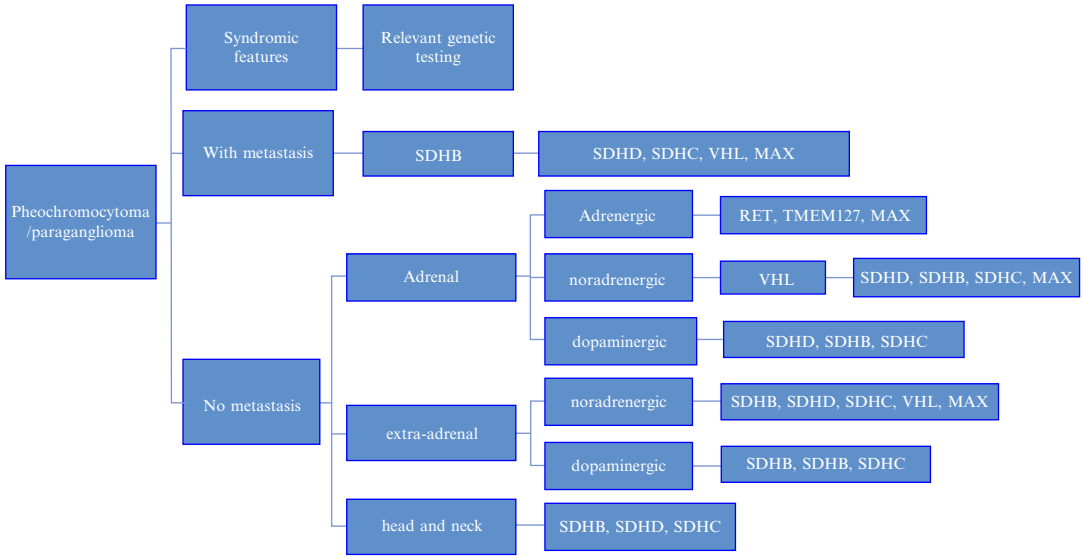
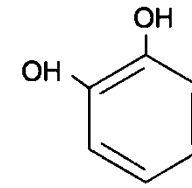


Fig. 1 Algorithm for genetic testing in patients diagnosed with pheochromocytoma (Adapted from reference Lenders et al. (2014))

5 Synthesis, Storage and Metabolism of Catecholamines

Fig. 2 Catechol ring (ortho-dihydroxybenzene)



The measurement of catecholamines and/or their by-products is the key in diagnosing pheochromocytoma. Although in the past the direct measurement of catecholamines was commonly used in the diagnosis, it is now considered a poor screening tool due to its relatively low sensitivity.

All catecholamines have a similar chemical structure with a catechol ring (ortho-dihydroxybenzene) and an amine group (Fig. 2).

Tyrosine is the initial substrate in the formation of catecholamines and is either derived from food or is synthesised in the liver from phenylalanine (Fig. 3). It subsequently enters chromaffin cells by active transportation and undergoes hydroxylation and decarboxylation to form various types of catecholamines. The rate-limiting step in catecholamine synthesis is the conversion of tyrosine to DOPA, which is regulated by the enzyme tyrosine hydroxylase. In managing patients with catecholamine-secreting neoplasms, inhibition of this rate-limiting step by tyrosine hydroxylase inhibitors (e.g. metyrosine) can inhibit the synthesis of catecholamines.

Subsequent to this rate-limiting step, dopamine is synthesised by further decarboxylation of DOPA by the enzyme, aromatic L-amino acid decarboxylase. It is then hydroxylated to form noradrenaline and stored as granules within the chromafin cells. It is subsequently released it to the cytoplasm of the chromaffin cells in the adrenal medulla, where phenylethanolamine N-methyltransferase (PNMT) converts it to adrenaline. Interestingly, PNMT is regulated by glucocorticoids and, due to the corticomedullary portal system in the adrenal gland, medullary PNMT-producing cells are exposed to high concentrations of cortisol, making the adrenal medulla the prime location for adrenaline-secreting adrenal tumours.

Once formed, these catecholamines are stored in electron-dense granules. Transport of

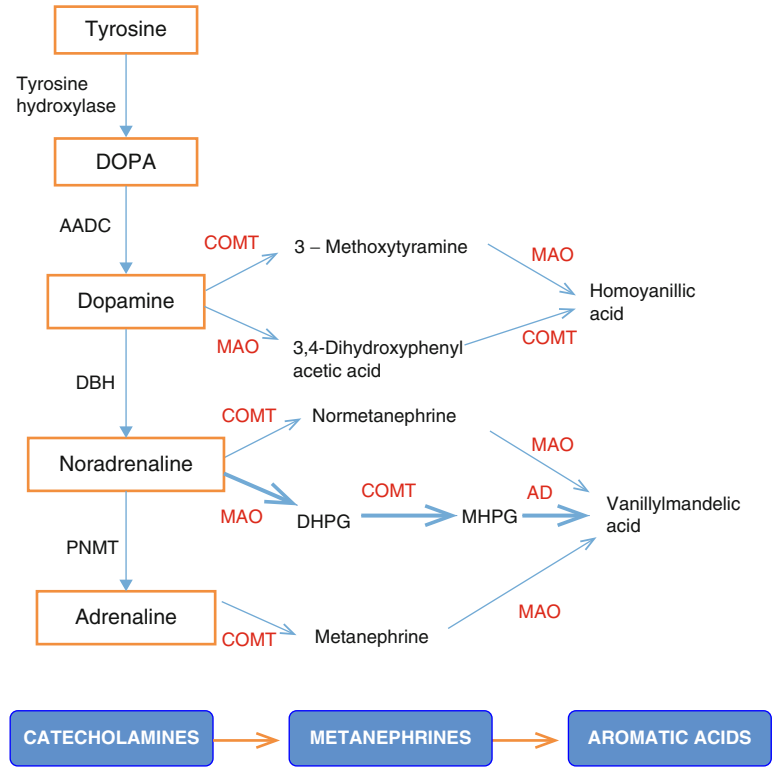


Fig. 3 Production of catecholamines (*AADC* aromatic L-amino acid decarboxylase, *DBH* dopamine B-hydroxylase, *PNMT* phenylethanolamine N-methyltransferase, *MHPG* 3-methoxy-4-hydroxyphenylglycol, *DHPG* 3,4-dihydroxyphenylglycol, *AD* aldehyde dehydrogenase)

substances into these granules is regulated by vesicular monoamine transporters (VMAT). Iodine-labelled MIBG (^{123}I or ^{131}I) is transported by VMAT into these storage granules and is a useful tool in localising (and treating) catecholamine-secreting pheochromocytoma/paraganglioma.

6 Biochemical Evaluation

Catecholamines have a short half-life, of approximately 10–100 s, in the plasma. The nerve terminals reuptake the catecholamines they produce themselves, while extra-neuronal catecholamines are metabolised by catechol-O-methyl-transferase (COMT) to form metanephrine and normetanephrine. Sympathetic nerves contain MAO, but not catechol-O-methyltransferase (COMT). Intraneuronal metabolism of norepinephrine leads to production of the deaminated metabolite, DHPG, but not the O-methylated metabolite, normetanephrine. Consequently, almost all of the DHPG in plasma has a neuronal source, whereas normetanephrine and metanephrine are derived exclusively from non-neuronal sources including chromaffin cells in the adrenal medulla (Eisenhofer et al. 2004). Normally the O-methylation pathway represents a minor route of catecholamine metabolism while deamination of noradrenaline within sympathetic nerves is the major pathway (Fig. 3). However, in patients with pheochromocytoma, intratumoral O-methylation pathway dominates catecholamine metabolism, leading to relatively large increases in production of the O-methylated metabolites compared with minor increases of the deaminated metabolites (Eisenhofer et al. 2004; Eisenhofer 2012).

Unfortunately, the short half-life of catecholamines makes it difficult to discriminate pathological overproduction from normal transient bursts of secretion during stress. Therefore, due to the short plasma half-life and intermittent nature of secretion, measurement of catecholamines can give a high rate of false

positive results, while sampling between bouts of paroxysmal release will cause false negatives. Most authorities, including major guidelines, recommend that either free plasma metanephrines or fractionated urinary metanephrines as the investigations of choice for the diagnosis of phaeochromocytoma. The recommended laboratory techniques are liquid chromatography with mass spectrometric or an electrochemical detection method (Lenders et al. 2014) Although plasma free metanephrine and normetanephrine are nearly as rapidly cleared from the circulation as their catecholamine precursors, they are superior to catecholamines for diagnosis as these metabolites are produced continuously from catecholamines leaking from storage vesicles into the cytoplasm where COMT then leads to conversion to metanephrine and normetanephrine. This process is not only continuous, but also independent of exocytotic catecholamine secretion, which in phaeochromocytomas can be intermittent or only active with low rates of secretion.

Plasma fractionated metanephrines have a high sensitivity, 96–100 %, with a specificity of 85–89 %, and is especially useful in diagnosing patients who carry a higher risk for habouring a phaeochromocytoma. High-risk patients, who would benefit from initial plasma metanephrine measurment, are patients with resistant hypertension, typical spells, a past history of phaeochromocytoma, genetic syndromes or a family history of a genetic syndrome, or an adrenal incidentaloma suggestive of a phaeochromocytoma. Apart from these, plasma measurements can be useful in children where 24-h urine collection is difficult. Due to its high sensitivity, a normal plasma metanephrine result will exclude the presence of a phaeochromocytoma in the above-mentioned high-risk patients. The only exceptions are seen in preclinical early disease or tumours with selective dopamine hypersecretion (Sawka et al. 2003). The plasma sample should ideally be drawn from a supine patient (fully recumbent for at least 20–30 min) and appropriate supine cut-offs should be used in the interpretation. In fact, it has been recently indicated that with a 'seated sampling' the diagnostic accuracy of the plasma test is no better, if not worse, than the urinary test (Lenders et al. 2014; Därr et al. 2014).

Twenty-hour fractionated urinary metanephrines are another investigation frequently used by clinicians. Perry et al. demonstrated that 24-h urine fractionated metanephrines using mass spectrometry provide excellent sensitivity (97 %) and specificity (91 %) for the diagnosis of a phaeochromocytoma. Therefore, it can be used in patients with a lower index of clinical suspicion as it has a higher specificity than the plasma measurement (Perry et al. 2007). Urinary metanephrines should include a urinary creatinine measurement to verify adequacy of urine collection, and assessments of the utility of random urine samples are in process. However, it should be emphasised that in practice there is probably little difference in the utility of plasma or urinary collections, with appropriate cut-offs, and the assay employed will often depend on local resources and experience.

7 Interfering Medications

Although metanephrine and normetanephrine are the preferred biochemical substances for diagnosis in comparison to catecholamines, their levels can be altered by several medications due to their effect on the metabolising enzymes, COMT and MAO, and uptake pathways. Tricyclic antidepressants (TCA) are well recognised to interfere with the assessment of metanephrines, and it is recommended to taper off and withhold TCAs and other anti-psychotics (except highly selective serotonin reuptake inhibitors) for at least 2 weeks prior to metanephrine analysis (Neary et al. 2011) (Table 4).

8 Tumour Localisation

Once catecholamine excess is biochemically confirmed, tumor localisation can be initiated by way of imaging. While imaging is almost always followed by biochemical confirmation, in patients with high risk factors such as a past history or genetic predisposition to phaeochromocytoma (eg. SDH mutation) there might be justification to proceed with imaging in the

Table 4 Medications that may cause falsely elevated results for catecholamine and metanephrine levels

Medications that cause pharmacodynamics interference and elevate levels (affect all assays)
Tricyclic antidepressants
Levodopa
Antipsychotic agents
Drugs containing adrenergic receptor agonists (e.g., decongestants)
Serotonin and noradrenaline reuptake inhibitors (duloxetine, venlafaxine)
MAO inhibitors
Amphetamines
Prochlorperazine
Reserpine
Phenoxybenzamine (elevate plasma and urinary normetanephrine)
Ethanol
Illicit drugs (e.g., cocaine, heroin) and withdrawal from these, and possibly cannabis.
Medications that cause analytical interference with some assays- (LC-ECD)*
Acetaminophen (a.k.a Paracetamol, elevate plasma and urinary normetanephrine)
Labetalol, sotalol (elevate urinary meta/ normetanephrine)
Buspirone (elevate plasma and urinary metanephrine)
Methyldopa (elevate plasma and urinary normetanephrine)
Sulphasalizine (elevate plasma and urinary normetanephrine)
Midodrine

**LC-ECD* Liquid chromatography with electrochemical or fluorometric detection

absence of compelling biochemical evidence. Some paragangliomas, especially in the head and neck region, can be biochemically silent and imaging with negative biochemistry is warranted in these instances as well.

As discussed previously, 90 % of phaeochromocytomas are adrenal in origin, while 10 % are extra-adrenal. Of these extra-adrenal phaeochromocytomas or paragangliomas, 80–95 % are within the abdomen and pelvis (superior and inferior para-aortic areas in the abdomen −75 %, urinary bladder- 10 %, thorax −10 %, head, neck, and pelvis –5 %) (Whalen et al. 1992). Therefore, CT scanning of the abdomen and pelvis following an adrenal protocol is the recommended initial imaging modality (Mantero et al. 2000). CT provides high tomographic resolution with a localisation sensitivity between 88 % and 100 %. On CT imaging, phaeochromocytomas can be homogeneous or heterogeneous, solid or cystic and with or without calcification. Phaeochromocytomas are notorious in being able to mimic the radiological features of adrenal carcinoma. Most (if not all) phaeochromocytomas have an attenuation greater than 10HU due to their lower fat content, while some can demonstrate very high attenuation due to haemorrhage (Sane et al. 2012; Blake et al. 2004).

The use of contrast agents during CT scanning has been an area of controversy for many years with concerns on risk of precipitating a hypertensive crisis; however, low-osmolar non-ionic contrast agents have been used safely in patients with phaeochromocytoma (Mukherjee et al. 1997), and this has more recently been confirmed (Baid et al. 2009). Phaeochromocytomas typically enhance avidly, indicating the rich capillary framework in the tumour, but nevertheless they can be heterogeneous with regions of absent enhancement due to cystic changes and necrosis. Contrast washout is useful in the evaluation of adrenal lesions, with an absolute contrast wash out of >60 % or a relative washout of >40 % at 15 min indicating a lipid-rich adenoma. Phaeochromocytoma, in its typical inconsistent nature, can have variable washout patterns, although the majority of phaeochromocytomas have a delayed contrast washout (Blake et al. 2004) (Fig. 4).

MRI is another useful tool in localising phaeochromocytomas. The most common MR imaging appearance of a phaeochromocytoma is of low signal intensity on T1 imaging and high signal intensity on T2-weighted imaging. They usually enhance avidly on T1-weighted imaging after gadolinium-enhancement. Although MRI lacks the superior spatial resolution of CT, it is useful to detect skull base and neck paragangliomas, for patients who cannot undergo CT scanning (metal clips, allergy to contrast, etc.), and for patients in whom exposure to radiation should be minimised (children, pregnant women, patients with known germline mutations undergoing regular screening) (Lenders et al. 2014; Jalil et al. 1998).

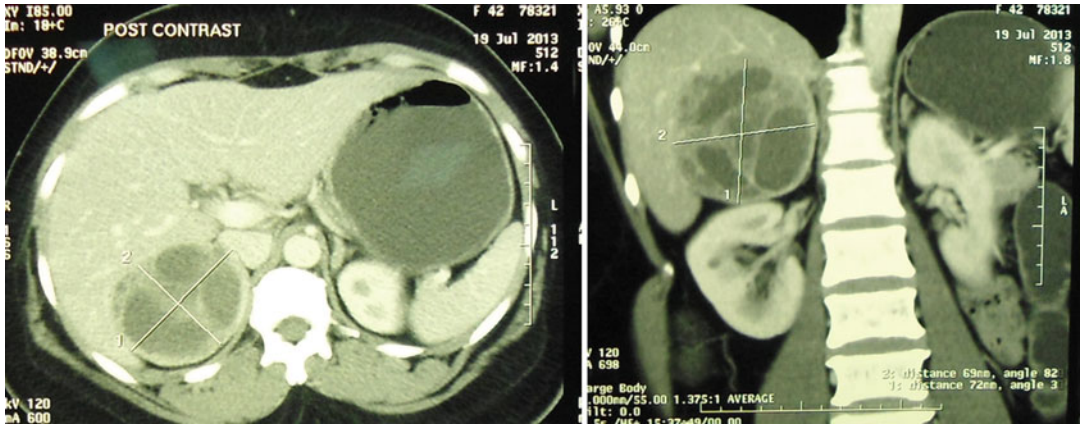


Fig. 4 Contrast enhanced CT scan of a young female presenting with hypertension showing a large, inhomogeneous, multiloculated mass with cystic and solid areas. A mass measuring 76 × 66 × 66 mm is seen in the right adrenal gland

Functional imaging is another widely used imaging modality for phaeochromocytomas. Meta-iodobenzylguanidine (MIBG) is a radiopharmaceutical agent that accumulates preferentially in catecholamine-producing cells and is transported into the electron-dense catecholamine storing granules via the transporter molecule VMAT. Radiolabelled MIBG is taken up by normal tissue innervated by the sympathetic system, such as heart, salivary glands, and tumours that express the neurohormonal transporters. ^{123}I-labelled MIBG has a sensitivity between 85 % and 88 % for phaeochromocytomas and between 56 % and 75 % for paragangliomas. Its specificity ranges from 70–100 % to 84–100 %, respectively (Berglund et al. 2001; Bhatia et al. 2008; Jacobson et al. 2010; Mozley et al. 1994). ^{123}I-MIBG allows better imaging when compared to ^{131}I-MIBG as its photon energy allows SPECT scanning which can greatly improve the sensitivity of the image. Therefore, ^{123}I MIBG remains the recommended agent for functional imaging in patients with phaeochromocytoma. Due to the fact that up to 50 % of normal adrenals take up MIBG asymmetrically, one should be aware of false positive results, especially when performed on a patient with normal biochemistry or after unilateral adrenalectomy (Jacobson et al. 2010). The major uses of MIBG imaging are confirmation that an adrenal lesion is a phaeochromocytoma, the identification of metastases, and for assessing suitability for ^{131}I-MIBG therapy. ^{123}I-MIBG imaging gives a valuable hint on the response to ^{131}I MIBG treatment in patients with metastatic pheochromocytoma or paraganglioma. Apart from this, ^{123}I MIBG can be used to detect occult metastasis in patients with increased risk for metastatic phaeochromocytoma or paraganglioma (eg, a large primary tumour, recurrent disease, and extra-adrenal or multifocal disease) (Lenders et al. 2014).

Table 5 Drugs that interfere with MIBG scanning

Tricyclic antidepressants
Prochlorperazine
Anti-psychotics
Cocaine
Amphetamines
Dopamine
Reserpine
Sympathomimetics
Labetalol
Ca^{++}-channel blockers (?increase uptake)

Prior to ^{123}I MIBG imaging, thyroid uptake of radioactive iodine must be blocked with iodide, usually nowadays in the form of potassium iodide. It is also important to bear in mind that certain medications can impair the uptake of MIBG and should be withheld for 2 weeks (Table 5).

Apart from MIBG, recent studies have identified several other functional imaging modalities including PET scanning using ^{18}F-fluorodopamine, ^{18}F-fluorodihydroxy-phenylalanine (^{18}F-DOPA), or ^{18}F-fluoro-deoxy-glucose (FDG). This is especially used in paragangliomas or metastatic disease including SDH-related tumours (Timmers et al. 2009). However, few of these are generally available. ^{18}F-FDG-PET can also be of use when other localising imaging techniques are negative as it is highly sensitive to these tumours which demonstrate increase glycolysis compared to aerobic metabolism, especially tumours showing SDH mutations, or rapidly growing metastatic tumours (Mamede et al. 2006).

Other functioning imaging modalities now being considered for localization are ^{111}In-pentetreotide scintigraphy in combination with CT/MRI and ^{68}Ga-DOTA-NOC. As both phaeochromocytomas and paragangliomas express somatostatin receptors to some extent, these somatostatin receptor scintigraphic studies have been shown to localise malignant, metastatic and extra-adrenal lesions very effectively, and can indicate the possibility of peptide radioreceptor therapy (Naswa et al. 2012).

9 Treatment of Pheochromocytoma in Adults

9.1 Perioperative Medical Management

Once diagnosed and localised, the treatment of choice in phaeochromocytoma is surgical removal. Surgical mortality in patients with undiagnosed pheochromocytoma' who undergo any surgery without preoperative medical therapy is high due to lethal hypertensive crises, malignant arrhythmias, and multi-organ failure. Adrenalectomy itself can release high levels of circulating catecholamines during surgery, leading to hypertensive crises and arrhythmias, even in normotensive and asymptomatic patients. Therefore, all patients with a hormonally-active phaeochromocytoma/paraganglioma should undergo preoperative adrenergic blockade and the first choice should be an alpha-adrenergic receptor blocker (Lenders et al. 2014). Unfortunately, there are no randomised head-to-head clinical trials to compare as to which alpha-blocker is most suitable. Phenoxybenzamine is an irreversible, non-selective, non-competitive, α-adrenoceptor blocker, with a longer duration of action due to its irreversible action. This should be initiated at least 7–14 days prior to surgery to ensure adequate α-blockade. Phenoxybenzamine is started at a dose of 10 mg twice daily and titrated up gradually till the patient is normotensive with no paroxysms of tachycardia or hypertension. The dose can be titrated up by 10–20 mg daily dose increments, going up to a maximum tolerable dose, which is generally a total daily dose of 1 mg/kg. The common side effects of phenoxybenzamine are postural hypotension with reflex tachycardia and dizziness, syncope and nasal congestion. It can also lead to inhibition of ejaculation, miosis and lassitude. Although the irreversible, prolonged inhibition caused by phenoxybenzamine offers effective adrenergic blockade during adrenal surgery, the prolonged action can contribute to hypotension in the first 24 h after tumour removal (Pacak 2007).

Due to the aforementioned difficulty with phenoxybenzamine, selective α_1-adrenergic blockers such as prazosin, terazosin or doxazosin are used in some centres. Although there are no head-to-head comparison studies, some retrospective studies have demonstrated that selective α1-adrenergic blockers are associated with lower diastolic pressure preoperatively, a lower incidence of reactive tachycardia, lower intraoperative heart rate, and better postoperative recovery with lower incidence of sustained postoperative hypotension (Prys-Roberts and Farndon 2002). However, there are other studies demonstrating no significant benefit in selective α_1-adrenergic blockers over phenoxybenzamine (Kocak et al. 2002). If these are used, prazosin is administered at 2–5 mg two or three times a day, terazosin at 2–5 mg per day, and doxazosin in doses of 2–8 mg per day. Some centres initially use phenoxybenzamine and subsequently change over to prazosin to avoid post-operative hypotension (Malchoff et al. 2004).

Beta-adrenergic blockers are useful preoperatively to control tachycardia only after the administration of adequate alpha-adrenergic blockade. As shown in Table 1, α1 receptor stimulation causes vasoconstriction while β2-receptor stimulation can cause peripheral vasodilatation; β-receptor blockade prior to α-blockade will cause α1-induced severe vasoconstriction without compensatory β2-induced vasodilatation, leading to hypertensive crises. Propranolol and atenolol are recommended for pre-operative use and should be initiated at least 3–4 days after the initiation of alpha blockade (Lenders et al. 2014). Although labetalol and carvedilol have combined α- and β-adrenoceptor effects, they are not recommended as their alpha:beta inhibition ratio is 1:7. Therefore, if used alone they can precipitate a hypertensive crisis, due to poor α-receptor inhibition. Some centres only add in β-antagonists if there is significant tachycardia.

Another agent that can be used is a calcium channel blocker. These drugs block catecholamines and cause calcium influx into vascular smooth muscle, thereby controlling hypertension and tachycardia. Calcium channel blockers can be used as a supplement to an adrenoceptor blocker in patients with inadequate blood pressure control or as a replacement for patients with severe side-effects on adrenoceptor blockers.

Metyrosine is an inhibitor of tyrosine hydroxylase, which is the rate-limiting step in catecholamine synthesis (Fig. 2). It can be used in combination with α-blockers for a short period before surgery to further stabilise blood pressure and blood loss during surgery (Steinsapir et al. 1997), but it is of limited availability.

Apart from adrenoceptor blockade, in patients with phaeochromocytoma it is vital to ensure adequate intravascular volume repletion as catecholamine excess causes blood volume contraction which is only 60 % corrected by the use of α-adrenergic blockade (Grosse et al. 1990). This is crucial to avoid severe post-operative hypotension, especially as these patients respond poorly to inotropes, due to pre-operative alpha and beta-receptor blockade. Retrospective studies demonstrate that a pre-operative high-salt diet, subsequent to initiation of an α-blocker, can reverse the volume contraction and reduce the post-operative hypotension (Pacak 2007). Apart from the high salt diet, 1–2 l of intravenous normal saline can be used to replete intravascular volume 24 h prior to surgery. However, one must be cautious not to fluid overload patients with kidney or heart failure.

Although there are no randomised studies on the pre-operative target blood pressure, a target blood pressure of less than 130/80 mmHg and a resting heart rate of 70 bpm are considered reasonable by most authorities.

9.2 Adrenalectomy and Surgical Outcome

Minimally-invasive laparoscopic adrenalectomy is the procedure of choice in patients with solitary intra-adrenal phaeochromocytoma without obvious radiological features of malignancy. However, for larger tumours of >6–8 cm or with features of local invasion, open adrenalectomy may be necessary (Lenders et al. 2014; Assalia and Gagner 2004). Paragangliomas are more likely to be found in areas difficult to access laparoscopically and are more frequently malignant. Therefore, paragangliomas are more likely to require open resection. Partial cortex-sparing adrenalectomy can be considered in patients with hereditary phaeochromocytoma (eg. MEN-2, VHL) and in patients who had undergone previous unilateral adrenalectomy.

Surgery of any catecholamine-secreting tumor is a high-risk procedure and should ideally be performed in a centre with an experienced surgeon, endocrinologist, and a team of anaesthesiologists. The most crucial part in the management of these patients is the multidisciplinary approach with the involvement of the surgeon, endocrinologist, anaesthetists and the intensive care specialists. Depending on the experience of the surgeon, either transperitoneal or a retroperitoneal laparoscopic approach can be taken. It is vital to avoid fracture of the tumour during dissection to avoid seeding into the tumour bed and peritoneal cavity. Intact specimen bags should be used for the safe retrieval of the resected tumour

and surgeons have successfully employed hand assistance or robot assistance for large, difficult to retrieve tumours (Brunaud et al. 2008). If cortical-sparing partial adrenalectomy is considered, devices such as ultrasonic shears can be used to minimise bleeding; 90 % of the patients who undergo cortical-sparing adrenalectomy remain glucocorticoid sufficient, especially so in patients with small tumours (Volkin et al. 2012). However, the disadvantage of cortical-sparing surgery is that inevitably there is some medullary tissue left behind which increases the rate of recurrence, with higher surgical complication risk during a second surgery.

As discussed above, patients should be satisfactorily blocked, as significant surges of catecholamines are inevitable during the surgery. Alpha and beta-adrenergic blockade should be continued until the morning of the surgery. Short-acting intravenous α- and β-adrenergic blocking agents should be available during surgery and agents such as fentanyl, ketamine and morphine should be avoided. Some anaesthetists use sodium nitroprusside to cause both arterial and venous dilatation and then fluid replace to maintain blood volume. Most anaesthetic gases can be used during surgery apart from halothane and desflurane. If bilateral adrenalectomy is planned, the patient should be on stress doses of hydrocortisone replacement peri-operatively. Cardiovascular and haemodynamic variables including intra-arterial pressure and heart rhythm must be monitored closely during and immediately follow surgery. If the patient has decreased cardiac reserve, monitoring of pulmonary capillary wedge pressure can be useful.

Acute hypertensive crises should be anticipated before or during surgery and should be treated with intravenous sodium nitroprusside, phentolamine or nicardipine. Sodium nitroprusside is a vasodilator and is ideal for intraoperative hypertension management due to its rapid onset and short duration of action. It should be initially started at a rate of 0.5–1.5 micrograms/kg/min, then increased in steps of 500 nanograms/kg/min every 5 min within range, 0.5–8 micrograms/kg/min. Intravenous phentolamine is a non-selective, short-acting α − adrenergic inhibitor, with a hypotensive response seen in 3–4 min following an intravenous bolus of 5 mg, which lasts for 10–15 min. Nicardipine is a dihydropyridine calcium channel blocker that relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It can be used as an intravenous infusion to maintain blood pressure during surgery. For the management of tachyarrhythmias, intravenous lidocaine, esmolol or labetolol can be used (Memtsoudis et al. 2005).

Hypotension may occur during and after surgical resection of a phaeochromocytoma, and the mainstay of treatment should be intravenous fluids and colloids, and only if necessary intravenous pressor agents can follow. Postoperative hypotension is less frequent in patients with adequate preoperative volume expansion and α-adrenergic blockade. Hypoglycemia should be anticipated in the immediate postoperative period with regular monitoring of blood glucose. Fluids given intravenously should preferably be 5 % dextrose to avoid hypoglycaemia. Patients with congestive cardiac failure or poor cardiac reserve should have close haemodynamic monitoring post-operatively with minimum blood pressure and heart rate fluctuations.

Although blood pressure normalises in the majority, some patients remain hypertensive for up to 4–8 weeks post-operatively. Hypertension can be persistent in a few patients due to resetting of the baroreceptors, structural changes to the blood vessels due to long-standing hypertension, damage to polar renal vessels during surgery, and coexisting essential hypertension. In terms of the catecholamine cardiomyopathy, the alarming ECG changes frequently normalise, but there is recent evidence based on MRI imaging showing persisting decreases in sytolic and diastolic function due to fibrosis (Ferreira et al. 2016).

9.3 Postoperative Follow-Up

Two weeks following the surgery all patients should be retested with a 24-h urinary fractionated metanephrines. If the levels are within normal limits, surgery can be considered complete. However, elevated levels of metanephrines following surgery may indicate

residual disease, which could be either residual adrenal disease or occult metastases.

All patients, including patients with normal metanephrines, should in our opinion have annual 24-h fractionated metanephrines evaluated for life. This is crucial to assess for metastatic disease, tumour recurrence in the adrenal bed and delayed appearance of multiple primary tumours. Several studies suggest a 10 % risk of tumour recurrence in the remnant adrenal gland (Yip et al. 2004). Moreover, higher recurrence rates should be expected in patients with familial disease, right-sided adrenal phaeochromocytoma, or paragangliomas (Young 2011; Amar et al. 2005). However, adrenal imaging is not routinely indicated, unless the metanephrines rise or in the follow-up of patients with a non-secretory primary lesion.

10 Histopathology

The typical histopathology of phaeochromocytomas and paragangliomas include chief cells with abundant granular cytoplasm and large vesicular nuclei and basophilic to amphophilic cells. However, some tumours may have scant cytoplasm with cellular and nuclear pleomorphism. Cytoplasmic hyaline globules and melanin-like pigment can be frequently seen. A prominent cell-nesting pattern called *zellballen* may be present with scattered ganglion cells. The chief cells are centrally located while Spindle shaped sustentacular or supporting cells are found periphery to the chief cell nests. Higher-grade tumours are characterized by a progressive loss in the ratio between chief cells and sustentacular cells with a decrease in the overall number of sustentacular cells (Barnes and Taylor 1990; Kliewer et al. 1989)

Immunohistochemical studies confirms the neuroendocrine origin of the tumour with positive staining of chief cells with chromogranin, synaptophysin and neuron-specific enolase (NSE). Moreover, sustentacular cells are negative for neuroendocrine markers and positive for molecular markers such as S100 acidic protein and GFAP. The absence of staining with certain molecular markers is of use when distinguishing phaeochromocytoma from other adrenal and renal tumours. For example, negative EMA staining in phaechromocytoma is useful to distinguish between renal cell tumours and negative staining with melan A, inhibin-α, calretinin, and keratin is helpful to distinguish between adrenocortical carcinoma. Further, phaeochromocytomas and paragangliomas are positive for chromogranin A and negative for melan A and keratin (Kliewer and Cochran 1989).

11 Malignant Phaeochromocytoma

Malignant phaeochromocytomas pose several challenges to the managing physician, starting from the diagnosis and leading up to the management. Identification of the malignant nature of a phaeochromocytoma remains a challenge as, unlike most malignant lesions, malignant phaeochromocytomas lack specific tumour and prognostic markers indicating malignancy: only the presence of metastases of chromaffin tissue at sites where no chromaffin tissue should be expected (eg. liver, bone, lymph nodes) establishes a definitive diagnosis of malignant phaeochromocytoma (Young 2011).

Several clinical, biochemical, radiological, genetic and histopathological clues can alert one to the potential of malignant disease in a patient with phaeochromocytoma. Malignant disease can present with features of catecholamine excess similar to benign phaeochromocytoma (eg. hypertension, funny spells etc.). However, malignancy can present with systemic and metastatic symptoms such as anorexia, weight loss and bone pain. If the malignant tumour is not well differentiated, the catecholamine production may not be complete, giving rise to absent or mild clinical features of catecholamine excess.

The anatomical site of the primary enterochromaffin tumour can give some idea of the possible malignant potential of a phaeochromocytoma. Some 10 % of phaeochromocytomas are malignant, while up to 35 % of mediastinal and abdominal paragangliomas are malignant. Head-and-neck paragangliomas have a lower

overall risk of malignancy at 4 %, while vagal and carotid body paragangliomas have a risk of 10–15 % (Eisenhofer et al. 2012).

Apart from the anatomical site, the genetic background of the patient adds to the potential malignant risk of a pheochromocytoma. SDHB gene carries the highest malignancy rates and patients with paragangliomas with this mutation should undergo screening for distant metastatic disease as part of the preoperative evaluation; VHL and MEN-2 carry a low risk of malignancy, 5 % or less.

Biochemistry can be useful in the differentiation between benign and malignant pheochromocytoma, although it is of limited value. Due to poor differentiation of the catecholamine biosynthetic pathway, they often do not complete the catecholamine production all the way up to noradrenaline (Fig. 3): therefore, they produce high levels of dopamine and its metabolites, particularly 3–methoxytyramine. Therefore, predominant production of 3-methoxytyramine suggests a malignant rather than a benign phaeochromocytoma (Eisenhofer et al. 2012; Parenti et al. 2012). Few other biochemical substances have been suggested to be associated with phaeochromocytoma. Chromogranin A is a protein co-secreted with catecholamines and is elevated in the presence of catecholamine secreting tumours. However, malignancy has been associated with very high serum chromogranin A levels (Grossman et al. 2006).

Similar to clinical and biochemical features, imaging offers limited clues in distinguishing malignant from benign phaeochromocytoma. The typical malignant features of adrenal imaging such as attenuation greater than 10HU, delayed contrast washout and inhomogeneous consistency, are seen in both benign and malignant phaeochromocytoma. However, radiology can be helpful in assessing the size and the location of the lesion. Tumours that are greater than 5 cm in size and extra-adrenal in location carry a higher risk for malignant disease than tumours that are small or have an adrenal location: size matters (Korevaar and Grossman 2011).

Somatostatin analogues labelled with gallium-68 (^{68}Ga-DOTATOC), ^{111}In-pentetreotide and ^{18}F-FDG are useful functional imaging modalities in identifying metastatic disease (Buchmann et al. 2007; Hofmann et al. 2001). Radiolabelled dopamine or dihydroxypheylalanine (DOPA), which is taken up by chromaffin cells, is another useful functional imaging modality, while PET with 6-[^{18}F]-fluoro-dopamine can detect metastatic phaeochromocytomas and paragangliomas with better sensitivity than ^{131}I-MIBG (Ilias et al. 2003).

Despite recent advances in histopathology and molecular markers, histological differentiation of benign and malignant phaeochromocytoma remains an area of difficulty as no single histological feature, by itself, is of significant value. Some evidence suggests that multifactorial analysis, combining several features, can be helpful in identifying significant metastatic risk. Several scoring systems have been proposed, considering growth patterns, invasion, cytology, mitotic activity and other tumour characteristics (Linnoila et al. 1990; Kimura et al. 2005). One of the most utilised scores is the "Pheochromocytoma of the Adrenal gland Scales Score" (PASS), proposed by Thompson et al. in 2002 (Table 6). Subsequent studies revealed that all malignant phaeochromocytomas had a PASS of

Table 6 Phaeochromocytoma of the adrenal gland scoring scale (PASS)

Feature	Value
Nuclear hyperchromasia	1
Profound nuclear pleomorphism	1
Capsular invasion	1
Vascular invasion	1
Extension into adipose tissue	2
Atypical mitotic figures	2
Greater than 3 of 10 mitotic figures high-power field	2
Tumor cell spindling	2
Cellular monotony	2
High cellularity	2
Central or confluent tumour necrosis	2
Large nests or diffuse growth (>10 % of tumour volume)	2
Total	**20**

Adopted from reference Thompson (2002)

>6 and a score of <4 suggested benign nature. Scores between 4 and 6 are indeterminate (Thompson 2002; Strong et al. 2008). Kimura has suggested a system bases on features of PAS but including Ki-67 as well as some non-histopathological criteria.

Several molecular markers associated with malignancy such as cyclooxygenase-2, secretogranin II-derived peptide, N-cadherin, vascular endothelial growth factor (VEGF), endothelin receptor type A (ETA), and type B (ETB) and telomerase have been identified. In particular, telomerase seem to be closely related to the malignant potential of paragangliomas (Parenti et al. 2012). Markers of proliferation such as Ki-67 based on the MIB-1 antibody can give additional information on the proliferative potential of the tumour. A Ki-67 of >2 % is considered a useful parameter predicting malignant potential (Liu et al. 2004). Recently, several micro-RNA expression studies have shown to act as biomarkers for differentiating benign and malignant phaeochromocytoma. Although promising, they need further evaluation with large cohort studies before the incorporation in to clinical practice (Parenti et al. 2012).

The treatment of malignant phaeochromocytoma can be a quite challenging and must be managed in a multidisciplinary setting. The prognosis can be variable with an overall 5-year survival rate of between 34 % and 60 %. The prognosis is worse in patients with lung and liver metastases rather than bone (Pacak et al. 2007). Surgical resection is the initial treatment with laparoscopic or open adrenalectomy with resection of locoregional lymph nodes. Surgical debulking is considered the mainstay of treatment for palliation, which can improve local or systemic symptoms related to catecholamine secretion and improves response to other therapeutic approaches. Liver metastases are treated with arterial or chemoembolisation as well as radiofrequency ablation (Maithel and Fong 2009).

Radio-metabolic treatment can be considered in patients with non-resectable lesions by using β-emitting isotopes coupled with MIBG or somatostatin analogues. ^{131}I-MIBG has been used for the treatment of malignant phaeochromocytoma over the last few decades and is usually preceded by diagnostic scintigraphy with ^{123}I-MIBG. About 60 % of metastatic sites are ^{131}I-MIBG avid with better responses seen in limited disease with soft-tissue metastases rather than diffuse disease with bone metastases (Loh et al. 1997). Radiolabelled somatostatin analogues are another form of treatment with the use of yttrium-90-DOTATOC (^{90}Y-DOTA-TOC) and lutetium-177- DOTA- TATE (^{177}Lu-DOTA- TATE). Both these can be used as potential treatment modalities if scintigraphy with either ^{111}In-pentetreotide or ^{68}Ga-DOTA-TOC shows high tumour uptake. Recent studies demonstrated that ^{68}Ga-DOTATATE PET/CT was significantly superior in detection rate to all other functional and anatomical imaging modalities and may represent the preferred future imaging modality in the evaluation of SDHB-related metastatic pheochromocytoma/paraganglioma (Janssen et al. 2015). Radionuclide treatment is low in toxicity with fewer side-effects compared to conventional cytotoxic agents and is useful in reducing the hormonal secretion and tumour bulk (Kwekkeboom et al. 2008; Forrer et al. 2008). Moreover, combination therapy with radiolabelled MIBG and somatostatin analogues can be considered as a future treatment option with lower toxicity and better efficacy (Sze et al. 2013).

The most used and effective anti-neoplastic chemotherapy regimen is a combination of cyclophosphamide, vincristine and dacarbazine (CVD). It is mainly considered in patients with locally advanced and/or metastatic lesion, unresectable tumours and disease resistant to the above mentioned treatment modalities (Andersen et al. 2011). Dacarbazine is an alkylating agent, which has the best chemotherapeutic effect on phaeochromocytoma. However, it remains unclear as to whether this combination regime prolongs survival. An oral alternative to dacarbazine, temozolomide has shown promise in a retrospective trial in the treatment of patients with malignant phaeochromocytoma/paraganglioma with SDHB mutation. The silencing of O-methylguanine-DNA methyltransferase

(MGMT) expression as a consequence of MGMT promoter hypermethylation in SDHB-mutated tumours has been considered as the possible mechanism of action of temozolomide (Hadoux et al. 2014). Neuroendocrine tumours have a rich vasculature and high levels of vascular endothelial growth factor (VEGF) expression. Therefore, agents inhibiting angiogenesis such as thalidomide has been evaluated for the treatment of malignant pheochromocytoma, in combination with temozolomide, but temozolomide alone is probably just as effective as the combination (Kulke et al. 2006). Molecular targeted therapy is another promising therapeutic option for malignant pheochromocytoma. Sunitinib, which is a potent inhibitor of multiple tyrosine kinase receptors, is an agent that has been considered patients with several studies showing a survival benefit. However, more data on the use of sunitinib will be released in the near future with the outcome of the First International Randomized Study in Malignant Progressive Pheochromocytoma and Paraganglioma (FIRST-MAPPP). Everolimus is an mTOR inhibitor which has not shown much efficacy when used on its own, but various animal and cell line studies have suggested that combinations of targeted therapy may be useful (Druce et al. 2009; Nölting et al. 2012; 2015).

Radiotherapy is another mode of treatment available for malignant pheochromocytoma. External beam radiotherapy is mainly considered for palliative treatment in pain management of bony metastases. It is important to bear in mind that adequate adrenergic blockade must be achieved prior to treatment as all these modalities can potentially precipitate a hypertensive crisis.

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