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Pheochromocytoma: presentation, diagnosis and treatment
Nicole Reisch\(^a\), Mariola Peczkowska\(^b\), Andrzej Januszewicz\(^b\) and Hartmut P.H. Neumann\(^c\)

Pheochromocytomas are rare, mostly benign catecholamine-producing tumors of chromaffin cells of the adrenal medulla or of a paraganglion. Typical clinical manifestations are sustained or paroxysmal hypertension, severe headaches, palpitations and sweating resulting from hormone excess. However, their presentation is highly variable and can mimic many other diseases. If remaining unrecognized or untreated, they can be a life-threatening condition. Therefore, the most important message of this review is to think of them. The diagnosis of pheochromocytomas depends mainly upon the demonstration of catecholamine excess by 24-h urinary catecholamines and metanephrines or plasma metanephrines. They are localized by a computed tomography scan and magnetic resonance imaging of the adrenal glands and abdomen; complementary \(^{123}\text{I}^-\text{metaiodobenzylguanidine scintigraphy and }^{18}\text{F}-\text{dihydroxyphenylalanine-positroneission tomography are available. Because approximately one out of four pheochromocytomas turn out to be hereditary entities, screening for genetic alterations is important. Laparoscopic and adrenal sparing surgical intervention following preoperative \(\alpha\)-blockade is the treatment of choice and usually curative. In malignant pheochromocytomas, radiotherapy and chemotherapy are palliative treatment options. This review provides an update on identification and management of pheochromocytomas, emphasizing current developments in diagnosis, including genetic testing, pathophysiology and treatment of pheochromocytomas. J Hypertens 24:2331–2339 © 2006 Lippincott Williams & Wilkins.

Introduction
Pheochromocytomas and abdominal paragangliomas are rare catecholamine-producing tumors with an estimated annual incidence of 2–8 per million population. The main occurrence occurs in the fourth and fifth decades of life affecting both genders equally. The prevalence in hypertensive patients is 0.2–0.4% \([1,2]\). Histologically, these tumors arise from chromaffin cells derived from the neural crest. Most pheochromocytomas (85–90\%) are located in the adrenal gland. Extra-adrenal pheochromocytomas of the sympathoadrenal neuroendocrine system are distributed along the paravertebral and para-aortic axis. They are found predominantly in the organ of Zuckerkandl (75\%), but they can also occur in thoracic, mediastinal, abdominal and pelvic locations \([3]\). The terminology is somewhat confusing and often differs between clinical and scientific use. According to their clinical manifestation in this review, we call tumors originating from the sympathetic neuroendocrine system pheochromocytomas, which can either be located in the adrenal medulla or extra-adrenal (nb. extra-adrenal pheochromocytomas are sometimes named functional paragangliomas by other groups). As paragangliomas, we refer to tumors found in the head and neck region (e.g. within the glomus caroticum), which derive from the parasympathetic system. Distinct from pheochromocytomas, paragangliomas according to this definition are usually not functioning (i.e. they do not produce excess catecholamines). This symptom-orientated terminology differs from the current WHO terminology, according to which pheochromocytomas always have an intra-adrenal origin and paragangliomas are located extra-adrenally and include catecholamine and non-catecholamine-producing tumors originating from chromaffin cells..

Pheochromocytomas and paragangliomas occur as sporadic tumors or in a familial context. Neumann et al. \([4]\) showed that close to 24\% of patients with pheochromocytomas and paragangliomas carry a germline mutation. This was confirmed by Amat et al. \([5]\) who even found 27\% carrying germline mutations. Therefore, the historically established ‘rule of tens’, stating that approximately 10\% of pheochromocytomas are hereditary, 10\% are malignant, 10\% are bilateral, 10\% are extra-adrenal, 10\% are not associated with hypertension and 10\% occur in children, is no longer valid concerning genetics \([6]\). Genetic screening nowadays is assigned a key role in diagnosis. The main syndromes associated with pheochromocytomas and paragangliomas are listed in Table 1 \([1,7–11]\).

Approximately 10\% of pheochromocytomas are bilateral tumors, most likely to be observed in children and patients...
In extra-adrenal pheochromocytomas and paragangliomas, neoplasms) and therefore require lifelong surveillance [13]. Women mostly malignant melanomas and cervix carcinoma, biliary tract cancers and central nervous system tumors, for developing other malignancies (men mostly for liver, adrenal pheochromocytoma face a four-fold increased risk 15% are malignant [12]. However, a Swedish study showed that patients with von Hippel-Lindau disease (VHL, 15–20%) type 2 A: Retinal and CNS haemangioendotheliomas Pheochromocytomas Endolymphatic sac tumors Epididymal cystadenomas B: + Renal cell cysts and carcinomas + Pancreatic neoplasms and cysts C: Pheochromocytomas only Neurofibromatosis type 1 (NF1) (3–5%) Multiple fibromas on skin Cafe au lait spots Lisch nodules of the iris Pheochromocytoma-paraganglioma syndrome (PGL, 70–80%) Head and neck tumors (Extra-adrenal) pheochromocytomas VHL type 2A-C is currently used as shown here. More correct is to add ‘pre-dominantly’ or ‘nearly always’. with familial tumors. Only 10–15% are malignant [12]. However, a Swedish study showed that patients with adrenal pheochromocytoma face a four-fold increased risk for developing other malignancies (men mostly for liver, biliary tract cancers and central nervous system tumors, women mostly malignant melanomas and cervix carcinomas) and therefore require lifelong surveillance [13]. In extra-adrenal pheochromocytomas and paragangliomas, the risk for malignancy is higher (29–40%) than the thumbrule of 10%, and an increased risk is also observed in women, at young age, and in tumors with more than 5 cm in size [7]. In most pheochromocytoma-associated syndromes, malignant pheochromocytomas are rare [MEN2, VHL, PGL 1, 4 (pheochromocytoma-paraganglioma-syndrom) except for SDHB-associated pheochromocytomas and paragangliomas with malignancy rates of 35% and NF1-associated disease with approximately 10% malignant tumors [2,10,11]. Distinguishing benign from malignant tumors by histopathological methods is still impossible in most cases. Until now, the only reliable criterion for malignancy is the presence of distant metastases. Local invasiveness, vascular and capsular invasion or a high mitotic index can indicate, but do not provide evidence for, malignancy [12]. There are several molecular markers, such as expression of human telomerase reverse transcriptase, heat shock protein 90, secretogranin II-derived peptide and numerous angiogenesis factors, that might provide diagnostic predictors of malignant behavior [12,14]. However, a reliable marker for the malignant potential of an individual tumor is not yet available.

### Table 1 Familial pheochromocytomas [1,7–9,11]

<table>
<thead>
<tr>
<th>Syndrome (prevalence of pheochromocytomas)</th>
<th>Gene</th>
<th>Genelocus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endocrine neoplasia Type 2 (MEN2, 30–60%)</td>
<td>Ret-protooncogene</td>
<td>10q11.2</td>
</tr>
<tr>
<td>Medullary thyroid carcinoma Pheochromocytoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: Hyperparathyroidism</td>
<td>VHL-tumor suppressor gene</td>
<td>3p25–26</td>
</tr>
<tr>
<td>B: Multiple neuromas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Von Hippel-Lindau disease (VHL, 15–20%) type 2 A: Retinal and CNS haemangioendotheliomas Pheochromocytomas Endolymphatic sac tumors Epididymal cystadenomas B: + Renal cell cysts and carcinomas + Pancreatic neoplasms and cysts C: Pheochromocytomas only Neurofibromatosis type 1 (NF1) (3–5%) Multiple fibromas on skin Cafe au lait spots Lisch nodules of the iris Pheochromocytoma-paraganglioma syndrome (PGL, 70–80%) Head and neck tumors (Extra-adrenal) pheochromocytomas</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VHL type 2A-C is currently used as shown here. More correct is to add ‘pre-dominantly’ or ‘nearly always’.

### Symptoms and clinical findings

Excess release of catecholamines and high levels of circulating catecholamines are responsible for the typical symptoms. Pheochromocytomas may secrete either noradrenaline or epinephrine but, usually, they release both of them with a predominance of noradrenaline. Rarely, they may also secrete dopa and/or dopamine. It is not known why the hormones are released intermittently and not continuously in most cases. Seventy-five percent of affected patients suffer from attacks weekly, others several times per day or just once every few months. The episodes occur suddenly and unexpectedly. In 80%, they last less than 1 h, then subside gradually and lead to exhaustion of the patient [3]. The attacks are characterized by headache (50%), sweating (50%) and palpitations (50–60%). However, recent studies showed that this classic triad occurs more rarely (15–24%) than usually assumed [15–17]. Even hypertension appears to be less frequent (60–70%) than stated in former studies [15–17]. Approximately one-half of the patients have permanent hypertension, the other 50% suffer from paroxysmal hypertension. Normotensive courses are typical for head and neck paragangliomas and more frequent in familial pheochromocytomas. Other adrenergic symptoms are summarized in Table 2 [3,18,19].

Because catecholamines can inhibit peristalsis, pheochromocytomas may be associated with severe constipation, pseudo-obstruction or ileus. Mesenteric artery vasoconstriction due to hypercatecholaminemia may result in ischemic enterocolitis with intestinal necrosis. In addition to a catecholamine excess, pheochromocytomas have been found to secrete neuropeptide Y or chromogranin A. Rarely, they may release vasointestinal peptide, serotonin, calcitonin, parathyroid hormone-related protein, adrenocorticotropic hormone (ACTH), neuron-specific enolase or interleukin-6 [2,3]. Asymptomatic pheochromocytomas are seldom, but may be

### Table 2 Clinical presentation of pheochromocytomas [3,18,19]

<table>
<thead>
<tr>
<th>Clinical symptoms</th>
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<tbody>
<tr>
<td>Headache, 50%</td>
</tr>
<tr>
<td>Sweating, 50%</td>
</tr>
<tr>
<td>Palpitations, 50–60%</td>
</tr>
<tr>
<td>Nervousness, anxiety</td>
</tr>
<tr>
<td>Flushing</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
<tr>
<td>Chest pain</td>
</tr>
<tr>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Warmth or heat intolerance</td>
</tr>
<tr>
<td>Pallor</td>
</tr>
<tr>
<td>Loss of weight</td>
</tr>
<tr>
<td>Polyuria</td>
</tr>
<tr>
<td>Polydipsia</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Hematuria, nocturia, bladder tenesmus</td>
</tr>
<tr>
<td>Cardiomyopathy</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
</tr>
<tr>
<td>Diarrhea</td>
</tr>
</tbody>
</table>
present in familial syndromes and approximately 5% of adrenal incidentalomas.

In malignant pheochromocytomas, there may also be symptoms from tumor infiltration and distant metastases. Patients develop metastases primarily in the skeleton as well as in lung and liver. In any case of sustained, paroxysmal hypertension or paradoxical hypertension despite antihypertensive therapy, especially during therapy with β-blockers, the diagnosis of pheochromocytoma has to be kept in mind and ruled out. New onset of hypertension under tricyclic antidepressive medication, severe symptomatic hypotension when starting therapy with α-blockers or severe retinopathy in newly-diagnosed hypertension may suggest pheochromocytoma. Other forms of secondary hypertension, such as renal artery stenosis, hypercortisolism and hyperaldosteronism, should be considered as differential diagnosis. Symptoms of pheochromocytoma can further be mimicked by hyperthyroidism, panic attacks, hypoglycemia and alcohol withdrawal symptoms. Sudden cessation of a clonidine of β-blocker therapy may also cause similar symptoms [3].

**Diagnosis**

**Laboratory diagnosis**

Pheochromocytomas are primarily diagnosed by biochemical evidence of catecholamine overproduction, either of the catecholamines themselves or their metabolites. Norepinephrine and epinephrine are metabolized to normetanephrine and metanephrine by the intra-cellular catecholamine-O-methyl transferase. The most frequently used screening method is the measurement of (fractionated) metanephrines in 24-h urine. According to recent studies, the highest test sensitivity (97–99%) is reached by measurement of plasma free metanephrines (specificity 82%) [20]. What makes them an optimal screening method is that they are produced and released continuously by the tumor, whereas measurement of basal plasma catecholamines due to variable and intermittent release is unsuitable for screening due to their periodic release [21–25]. Due to its high sensitivity, the assessment of plasma free metanephrines is a powerful method to rule out the diagnosis of pheochromocytoma in highly suspicious cases. In multiple endocrine neoplasia type 2 (MEN2) patients, substantially higher metanephrine concentrations, often but not always with additional increase in normetanephrine, have been reported, whereas tumors in von Hippel–Lindau syndrome (VHL) patients have been reported to be characterized by increases in normetanephrine, but not in metanephrine concentrations [26–29]. Therefore, this provides high specificity in this subgroup of patients. In summary, screening therefore generally should include measurement of either or both urinary fractionated metanephrines and plasma free metanephrines. To confirm borderline test results, the clonidine suppression test is applied rarely. In practice, we often perform directly imaging methods and search for a tumor in these cases.

However, the restricted availability of the measurement of plasma free metanephrines leads to different recommendations for optimal biochemical screening algorithms. In most clinical environments, measurement of plasma free metanephrines is not yet available for routine diagnostic and therefore measurement urinary fractionated metanephrines and urinary catecholamines remain the diagnostic test of choice [30–32]. Table 3 provides a summary of the sensitivity and specificity of biochemical tests for diagnosis of pheochromocytoma according to Lenders et al. [20].

It is further important to know that various drugs interfere with test results by interfering with the assay or affecting catecholamine synthesis, release or metabolism [3]. Drug-induced false-positive test results may be observed in patients taking tricyclic antidepressants, high-dose diuretics, levodopa and theophyllin. Moreover, caffeine and nicotine consumption both lead to elevated catecholamine levels. Decreased catecholamine concentrations can be found due to reserpine. Angiotensin-converting enzyme inhibitors, calcium channel blockers and low-dose diuretics do not significantly influence the test results. Because catecholamines are more stable at low temperature and low pH, urine collection for measurement of catecholamines is recommended to be refrigerated and acidified (pH < 3). For determination of metanephrines in urine, this is not necessary but it will not bias the measured metanephrine concentration. To detect inadequate collection, creatinine should be measured in the urine samples and checked for plausibility [22]. There is hardly any indication for selective catheterization of the left and right adrenal veins for catecholamine measurement; only extremely rarely will it be helpful in cases with a negative 123I-metaiodobenzylguanidine (MIBG) scan and unclear computed tomography (CT)/magnetic resonance imaging (MRI). It is crucial to perform this procedure only during α-blockage.

**Table 3** Comparison of biochemical tests [20]

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Hereditary</td>
<td>Sporadic</td>
</tr>
<tr>
<td><strong>Plasma</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free metanephrines</td>
<td>97</td>
<td>99</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>69</td>
<td>92</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fractionated</td>
<td>96</td>
<td>97</td>
</tr>
<tr>
<td>metanephrines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Catecholamines</td>
<td>79</td>
<td>91</td>
</tr>
<tr>
<td>Total metanephrines</td>
<td>60</td>
<td>88</td>
</tr>
<tr>
<td>Vanillylmandelic acid</td>
<td>46</td>
<td>77</td>
</tr>
</tbody>
</table>
Imaging

Localization diagnosis is based on imaging methods of and CT scans and/or MRI. A CT scan can detect pheochromocytomas at least 0.5–1.0 cm in diameter. The sensitivity for detecting adrenal pheochromocytomas via a CT scan reaches 85–94%, and is approximately 90% for extra-adrenal localizations. The advantages of CT scans are their cost effectiveness and high sensitivity. In adrenal tumors, unenhanced CT followed by contrast-enhanced CT and delayed contrast-enhanced CT imaging yields a sensitivity of 98% and a specificity of 92% [3,22,26,33,34]. MRI, on the other hand, provides superior contrasting effects in soft tissues and therefore may be better for differentiating pheochromocytomas from adrenal adenomas. It allows better assessment of the relationship of the tumor to its environment, particularly to exclude vessel invasion. Furthermore, iodide contrast agent is not necessary and the method does not use radiation [33]. MRI is very sensitive in localizing adrenal pheochromocytomas (93–100%). In extra-adrenal, metastatic and recurrent pheochromocytomas, it yields a sensitivity of 90%. However, its specificity often is substantially lower (50%) [33]. Complementary to a CT scan or MRI, 123I-MIBG scintigraphy is a highly specific method (alternatively 131I-MIBG can be used, but with poorer imaging quality [35]). MIBG a guanethidine analogue, resembling norepinephrine in its molecular structure, is labelled with 123I and taken up by peripheral sympathetic nerve endings and the adrenal medulla and, to some extent, actively transferred into catecholamine storage vesicles [33]. For diagnostic purposes, 123I-MIBG with a half-life of 13 h is applied intravenously and body scans are performed after 4 h and 24 h. The thyroidal resorption of 123I should be inhibited by previous application of perchlorate. The main goal of 123I-MIBG scintigraphy is to functionally confirm tumor tissue that has been localized via CT scan or MRI. It is also a helpful tool to diagnose extra-adrenal pheochromocytomas and remaining tumor tissue after surgery. The specificity of this method is very high (95–100%); however, its sensitivity is significantly lower (77–90%) [22,33]. Because several drugs (e.g. tricyclic antidepressants, labetalol, specific calcium antagonists) may interfere with tumor uptake of 123I-MIBG, they should be discontinued before imaging [36]. In malignant pheochromocytomas 111In-octreotide analogue provides another method for detecting metastasis. Compared to 123I-MIBG scintigraphy, it is substantially inferior concerning sensitivity; however, in malignant tumors, it may reveal metastasis that are not seen in 123I-MIBG scintigraphy due to histological dedifferentiation or bleeding [26,33,37,38]. If the above-mentioned imaging methods fail to detect pheochromocytomas, positron emission tomography (PET) imaging with 18F-fluorodeoxyglucose (FDG), 18F-dihydroxyphenylalanine (18F-DOPA) [39,40], 18F-fluorodopa (18F-DOPA) [41,42] or 11C-hydroxyephedrine [43] can be performed. Whereas FDG-PET is a non-specific method, 18F-DOPA- and 11C-hydroxyephedrine-PET provide high sensitivity and specificity because of take-up into catecholamine-producing cells [26]. 11C-hydroxyephedrine-PET yields good results; however, due to the short half-life of the 11C-isotope, it is hardly suitable for whole body scans [39]. 18F-DOPA-PET may reach up to 100% sensitivity and specificity [41,42].

Genetic diagnosis

To date, germline mutations in five genes have been described, leading to several familial disorders associated with pheochromocytoma [44]. An activating mutation of the RET proto-oncogene, coding for a tyrosine kinase receptor that transduces signals associated with growth and differentiation, leads to MEN2 [9]. An abnormal VHL gene, a tumor suppressor gene, is responsible for VHL [8,45–49]. Mutations of the neurofibromatosis type 1 gene (NF1) cause von Recklinghausen’s disease [48,50] and hereditary pheochromocytoma-paragangliomas syndrome is associated with mutations in succinate dehydrogenase (SDH) subunit genes SDHB and SDHD [11,44,51], comprising portions of mitochondrial complex II. The main clinical manifestations of these family disorders are summarized in Table 1. All syndromes are based on autosomal dominant inheritance pattern with variable penetrance. Pheochromocytomas are not always present, the frequency of pheochromocytomas in patients with MEN2 is approximately 30–60% [34], 15–20% in patients with VHL [34,52] and 3–5% in patients with NF1 [34,48]. According to the literature SDHB and SDHD mutation carriers have a very high risk of developing tumors. Neumann et al. [51] reported a penetrance of pheochromocytomas/paragangliomas in SDHB and SDHD mutation carriers of approximately 80% at age 50 years [51]. According to Benn et al. [53], a percentage of 80% of penetrance is reached in SDHB mutation carriers only at the age of approximately 70 years [53]. Neumann et al. [51] and Benn et al. [53] consistently report earlier ages of disease onset in SDHD compared to SDHB mutation carriers. Mutations of the SDHD gene are associated mainly with paragangliomas in the head and neck and multifocal disease. SDHB mutation carriers, however, develop in up to 35% malignancies and may also develop extraparaganglial neoplasias, including renal cell and thyroid carcinomas [51]. Pheochromocytomas in MEN2, VHL and NF1 disorders usually are not the first clinical manifestation and are more likely to be benign and bilateral [34].

In this context, genetic testing is essential to identify mutation carriers of hereditary pheochromocytoma at an early stage of the disease or even before any symptoms may appear [11]. This is very important for patients as well as for potential carriers among their relatives. Complete genetic testing may thus allow careful imaging and screening for pheochromocytomas, paragangliomas and for other tumors that occur in the distinct
pheochromocytoma-associated syndromes. Sometimes, a careful work-up of the family allows tumor diagnosis even at early, asymptomatic stages that would otherwise be missed. The chances for curative treatment of pheochromocytoma, but also of associated tumors (such as medullary thyroid cancer in MEN2 with pheochromocytoma as first manifestation), increase with early diagnosis due to genetic testing. Because up to 25% of apparently sporadic pheochromocytomas turn out to be hereditary, genetic testing should also be performed in these patients [4]. Other studies [5] demonstrate that, in more than 50% of apparently sporadic tumors, the hereditary disease may be suspected even before genetic testing if both patient and family history are carefully assessed. This emphasizes that the sequence of genetic testing should be adapted to clinical features. Extra-adrenal pheochromocytomas and paragangliomas, for example, often occur in carriers of SDHB and SDHD mutations. In VHL and NF1 patients, extra-adrenal localization of pheochromocytomas is also known; however, it is very rare in MEN2. If intra- and extra-adrenal pheochromocytomas and/or paragangliomas occur in the same patient, this hints towards pheochromocytoma-paraganglioma syndromes (PGLs) that are linked to mutations of the succinate dehydrogenase subunits SDHD and SDHB [11,51]. Renal tumors are found in 25% of patients with VHL; therefore, screening is first focused on mutations in the VHL gene. Pheochromocytomas in children are also highly suspicious to be due to VHL gene mutations. In malignant pheochromocytomas, the first target of genetic analysis are SDHB mutations because malignancy is reported in 35% in these cases [10,11,51]. Vice versa, according to our experience, 24% of patients with malignant pheochromocytoma have an underlying SDHB mutation (unpublished data). To improve the data base for incidence and prevalence of these syndromes as well as the frequency of distinct symptoms, the clinician should always aim at including all patients in population-based registers; for example the Freiburg–Warsaw Pheochromocytoma Registry [4,51,54]; contact H. P. H. Neumann (e-mail: neumann@medizin.ukl.uni-freiburg.de) or Andrzej Januszewicz in Warsaw, Poland (e-mail: drand@mp.pl). Other helpful contacts are for example Marta Barontini in Buenos Aires, Argentina (e-mail: mbarontini@cedie.org.ar), Maurizio Castellano in Brescia, Italy (e-mail: castella@med.unibs.it), Jacques Lenders in Nijmegen, the Netherlands (e-mail: j.lenders@aig.umcn.nl), Massimo Manelli in Florence, Italy (e-mail: m.mannelli@dfc.unifi.it), Giuseppe Opocher in Padua, Italy.

Management of pheochromocytoma

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Fig. 1

**Diagnostic procedure in pheochromocytomas.** The authors usually do not perform a clonidine test but proceed directly to imaging. However, the authors recommend adrenal sparing surgery also in these cases because familial origin of the tumor mostly is not yet excluded at the time of surgery and hereditary pheochromocytomas often present with only one tumor. CT, computed tomography; MRI, magnetic resonance imaging; \(^{123}\)I-MIBG, \(^{123}\)I-metaiodobenzylguanidine; PET, position emission tomography.
Preoperative pharmacological therapy
Before surgical intervention, adrenergic α-blockers must be applied sufficiently in dose and duration (7–14 days) to prevent hypertensive crisis and ensure blood pressure control. It is recommended to document normotension in a 24-h blood pressure profile before surgery. The substance of choice is phenoxybenzamine, a non-selective α-blocker [55,56]. The given dose is gradually increased over a period of 14 days, starting off with 10 mg twice a day. Under tight blood pressure control, the dose is increased by 10 mg per day up to 1 mg/kg per day given in three to four individual doses [56]. In most cases, 30–60 mg/day are sufficient. This treatment aims for normotension and prevention of hypertensive crisis, which should be documented preoperatively in a 24-h blood pressure protocol.

Negative side-effects might be tachycardia, orthostatic hypotension, gastrointestinal problems or swelling of nasal mucosa due to effective α-blockage. The last phenoxybenzamine dose is applied in the evening before surgery. Adrenergic blockage of α1-receptors with prazosin or doxazosin can also be performed [57]; however, documented experience is limited and therefore they are considered as second choice treatment options. Gradual dose increment from 1 to 16 mg once a day is necessary here, too [56]. β-blockers must only be applied after sufficient α-blockage as they might provoke vasoconstriction with marked blood pressure increments due to their blockage of β1-receptors and inhibition of any vasodilatating effect of epinephrine [58]. β-blockers are preferentially used to treat tachycardia or supraventricular dysrhythmias. This specific effect is mediated by β1 receptors. Therefore, selective β1-receptor blockers as atenolol and bisoprolol are recommended for treatment. Hypertensive crises are controlled with nitroprusside, nitroglycerine, phentolamine or urapidil. Continuous hypertension after tumor removal can indicate residual tumor tissue or metastases. It is also possible that the patient suffers from essential hypertension or coexisting renal artery stenosis regardless of his pheochromocytoma or that the hypertension caused by pheochromocytoma led to structural vessel adaptation [26].

Surgical therapy
Laparoscopic or retroperitoneoscopic minimal invasive removal of intra- and extra-adrenal pheochromocytomas now is the gold standard [59–63]. The advantages of minimal invasive surgery are less release of catecholamines during surgery than in open adrenalectomy, more rapid recovery, a cosmetically more satisfying result, a reduced need for postoperative analgesies and a shorter hospital stay. Bilateral total adrenalectomy yields an increased morbidity and mortality resulting from primary adrenocortical insufficiency. As a guideline, adrenal pheochromocytomas should be removed sparing the normal adrenal cortex; this recommendation is based on the fact that many patients with inherited conditions present initially with only one tumor and that genetic testing is currently so time-consuming that this cannot be completed before surgery. In bilateral sporadic and hereditary pheochromocytomas, adrenal sparing surgery in centres providing the necessary expertise preserving adrenocortical function should also be favoured [64]. To verify sufficient postoperative adrenocortical function, an ACTH stimulation test should be performed. All patients should be followed-up yearly for at least 10 years after surgery [65]. Because hereditary-type tumors are at higher risk for recurrences after adrenal sparing surgery, long-term follow-up and continuous surveillance is essential [26,66,67].

Therapy of malignant pheochromocytomas
The therapy of malignant metastatic pheochromocytoma is based on surgery, chemo- and radiotherapy aiming at tumor debulking and blockade of endocrine activity of tumors. In most cases, tumor tissue still remains after surgery, and thus surgery rarely is a curative option. As well as in cases not suitable for surgery, 131I-MIBG can be used as therapeutical option, given that the tumor shows uptake of MIBG: This may yield partial remission in 24–54% of patients; in rare cases, even complete remission has been reported [12,14]. Treatment with 131I-MIBG is well tolerated and can be repeated several times. Dose, therapy intervals and the number of therapy cycles have to be determined individually. Until now, there are no standardized guidelines on therapy with 131I-MIBG. 131I-MIBG therapy helps to prolong survival as well as achieve relief of symptoms [68]. If 131I-MIBG uptake is low, octreotide is another therapeutic option because several pheochromocytomas express type 2 and 3 somatostatin receptors. The available data on this issue are rare and inconsistent [14]. Another newly-practiced option is the application of high-dose 131I-MIBG in malignant pheochromocytomas [69,70]. In case of no...
radionuclide uptake or no satisfactory clinical response, chemotherapy is possible. Although there is no evidence-based chemotherapy protocol for malignant pheochromocytomas, the most widely employed regime has been reported by Averbuch et al. [71] (Table 4).

The CVD (cyclophosphamid, vincristine, dacarbacin) schedule was reported to yield complete and partial response rates of 57% and complete and partial biochemical responses in 79% of patients [71]. There are also hints for beneficial and additive effects of a combined regime of chemotherapy and 131I-MIBG therapy [70,72]. In case of bone metastasis, radiotherapy to stabilize and prevent pathologic fractures is performed. Another aspect of the therapeutic concept in malignant pheochromocytomas is the symptomatic control of catecholamine production. In excessive catecholamine concentrations, α-methyl-paratyrosine can be applied additionally; however, it should be used very carefully due to its negative side-effects [14,73]. Based on newly-discovered molecular mechanisms of tumorogenesis, promising targeted therapies might be developed (e.g. inhibition of heat shock protein 90, which is overexpressed in malignant pheochromocytomas). Other possible approaches could be the human telomerase reverse transcriptase or anti-angiogenic drugs [14]. The therapeutic algorithm is shown in Fig. 2.

**Prognosis**

In benign pheochromocytomas, the 5-year survival rate is above 95%, recurrences occur in less than 10% of cases [12]. Due to the low incidence of malignant pheochromocytomas, there are rather single case reports than...
larger series of patients and these indicate very different courses of disease.

Against this background and the necessity of evidence-based, multicentred and multidisciplinary approaches for research in this field, the Pheochromocytoma REsearch ORganization (PRESSOR) was founded in November 2003. The main goal of this consortium is to work out consensus guidelines for diagnosis and therapy of benign and malignant pheochromocytoma and paraganglioma and to create an international platform of discussion between expert groups working on these rare diseases.

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