Pheochromocytoma: Current Approaches and Future Directions

JOEL T. ADLER, a* GOSWIN Y. MEYER-ROCHOW, b,c* HERBERT CHEN, a DIANA E. BENN, c
BRUCE G. ROBINSON, c,d REBECCA S. SIPPEL, a STAN B. SIDHIU, b,c

aSection of Endocrine Surgery, Department of Surgery, University of Wisconsin, Madison, Wisconsin, USA; bEndocrine Surgical Unit, University of Sydney, cCancer Genetics, Kolling Institute of Medical Research, and dDepartment of Endocrinology, University of Sydney, Royal North Shore Hospital, New South Wales, Australia

Key Words. Pheochromocytoma • Management • Familial pheochromocytoma • Adrenal gland

Disclosure: H.C. has received honoraria from Novartis. The content of this article has been reviewed by independent peer reviewers to ensure that it is balanced, objective, and free from commercial bias. No financial relationships relevant to the content of this article have been disclosed by the authors, planners, independent peer reviewers, or staff managers.

LEARNING OBJECTIVES

After completing this course, the reader should be able to:

1. Use current practice methods in the diagnosis of pheochromocytomas.
3. Evaluate the current molecular research that contributes to the treatment of pheochromocytomas.

ABSTRACT

Pheochromocytomas are rare catecholamine-secreting tumors that arise from chromaffin tissue within the adrenal medulla and extra-adrenal sites. Because of the excess secretion of hormones, these tumors often cause debilitating symptoms and a poor quality of life. While medical management plays a significant role in the treatment of pheochromocytoma patients, surgical excision remains the only cure. Improved medical management and surgical techniques and an increased understanding of hereditary disease have improved the outcome of pheochromocytoma patients with benign disease; however, the outcome of patients with malignant disease remains poor. In this review, we discuss the presentation, diagnosis, management, and future directions in the management of this disease. The Oncologist 2008;13:779–793

INTRODUCTION

First described in 1886 by Fränkel, pheochromocytomas are rare catecholamine-secreting tumors derived from the chromaffin cells of the embryonic neural crest [1, 2]. These tumors can occur anywhere that sympathetic nervous tissue is found. While most pheochromocytomas arise in the ad-
renal medulla, there are also extra-adrenal pheochromocytomas (paragangliomas) of the abdomen, pelvis, thorax, and neck. Although these tumors are similar in origin, the clinical manifestation, prognosis, and management differ. The incidence of pheochromocytoma is <0.5% in patients with hypertensive symptoms [3] and can be as high as 4% in patients with adrenal incidentalomas [4]. Referrals for pheochromocytoma have been reported to be increasing, likely as a result of improved detection [5].

Because of excess secretion of the hormones epinephrine, norepinephrine, dopamine, and others, patients with pheochromocytoma often experience debilitating symptoms and have a poor quality of life. Treatment for benign and malignant disease is surgical resection, while chemotherapeutic options for malignant disease remain poor. Recent advances in diagnostic imaging, pharmacologic treatment, surgical technique, and molecular profiling have contributed to a better understanding of the natural history of this disease. This review summarizes the presentation, diagnosis, surgical intervention, postoperative management, and future directions in the treatment of benign and malignant pheochromocytomas.

**CLINICAL PRESENTATION**

Health care providers frequently learn that pheochromocytoma is the “tumor of tens:” 10% are extra-adrenal, 10% are bilateral, 10% are malignant, 10% are found in asymptomatic patients, and 10% are hereditary [6]. The recent description of mutations of the succinate dehydrogenase gene (SDH) has demonstrated a much stronger hereditary component than formerly thought [7]. Currently, up to 24% of pheochromocytomas may have a genetic predisposition [8, 9].

**“Classic” Presentation**

The classic triad of pheochromocytoma presentation is episodic headache, sweating, and palpitations [10, 11]. Persistent hypertension is frequently considered part of the presentation. As to be expected, these symptoms are not always present and certainly do not always constitute a diagnosis. In a retrospective study, blood pressure anomalies were associated with the discovery of pheochromocytoma in 51% of cases, while headaches and palpitations were found in 24% of patients [12]. While pheochromocytoma is frequently considered in cases of persistent hypertension, it accounts for <0.5% of these cases [3, 13]. Pheochromocytoma is typically found with a diverse set of symptoms, which may include anxiety, chest and abdominal pain, visual blurring, papilledema, nausea and vomiting, orthostatic hypotension, transitory electrocardiographic changes, and psychiatric disorders (Table 1) [14–16].

Occasionally, patients have normotensive, or “asymptomatic,” pheochromocytomas, which are frequently discovered incidentally. The prevalence of an asymptomatic pheochromocytoma is estimated to be 21% [17], and retrospective studies have shown no difference in demographic, radiographic, and pathologic characteristics in sporadic tumors [18, 19]. The reasons for this are unknown, but some have proposed that the cardiovascular system becomes desensitized to circulating catecholamines [18]. Patients with a genetic predisposition to pheochromocytoma tend to be younger, have smaller tumors, and are more likely to be normotensive [13].

**The Adrenal Incidentaloma**

With widespread application of abdominal imaging, an increasing number of adrenal masses are being found incidentally. In a Mayo Clinic study, 3.4% of all abdominal computed tomography (CT) scans performed over a 5-year period revealed an adrenal mass. Once all other known causes of the masses were excluded, 0.4% of all scans revealed adrenal incidentalomas >1 cm in size [19]. Autopsy studies have shown an adrenal mass prevalence of approximately 8% [20]. These data suggest that adrenal masses are a relatively common phenomenon. In an attempt to characterize how many of these are pheochromocytomas, a large retrospective series from Italy found that 4.2% of all adrenal incidentalomas were pheochromocytomas [4].

An adrenal mass in a patient with a history of cancer presents a diagnostic challenge [21, 22]. It is becoming increasingly recognized that these lesions are not always metastases and must be thoroughly evaluated [23]. In a se-

---

**Table 1. Signs and symptoms of pheochromocytoma**

<table>
<thead>
<tr>
<th>Symptom</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Tremulousness</td>
</tr>
<tr>
<td>Pallor</td>
</tr>
<tr>
<td>Chest and abdominal pain</td>
</tr>
<tr>
<td>Visual blurring</td>
</tr>
<tr>
<td>Papilledema</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td>Weight loss</td>
</tr>
<tr>
<td>Polyuria</td>
</tr>
<tr>
<td>Polydypsia</td>
</tr>
<tr>
<td>Heat intolerance</td>
</tr>
<tr>
<td>Orthostatic hypotension</td>
</tr>
<tr>
<td>Constipation</td>
</tr>
<tr>
<td>Transitory electrocardiographic changes</td>
</tr>
<tr>
<td>Hyperglycemia</td>
</tr>
</tbody>
</table>
ries of 81 patients with a history of malignancy and without known hereditary causes, five (6.7%) patients had sporadic pheochromocytomas [24]. After excluding patients with hereditary syndromes, another retrospective series found that one in four isolated adrenal lesions in patients with a history of cancer was a pheochromocytoma [25]. We agree with others and encourage a thorough evaluation of all patients with an isolated adrenal mass [26, 27].

Familial Pheochromocytoma
Prior to 2000, it was generally accepted that 10% of pheochromocytomas were associated with familial syndromes; however, it is now recognized that the frequency of germline mutations in apparently sporadic presentations is as high as 15%–24% [8, 28, 29–32]. Familial pheochromocytomas are often multifocal or bilateral and generally present at an earlier age than sporadic pheochromocytoma [33, 34]. Germline mutations in six genes have been associated with familial pheochromocytoma, namely, the von Hippel-Lindau gene (VHL), which causes von Hippel-Lindau (VHL) syndrome, the RET gene, leading to multiple endocrine neoplasia type 2 (MEN-2), the neurofibromatosis type 1 gene (NF1), associated with neurofibromatosis type 1 (NF1) disease, and the genes encoding subunits B and D (and also rarely C) of mitochondrial succinate dehydrogenase (SDHB, SDHD, and SDHC), which are associated with familial paraganglioma/pheochromocytoma (Table 2).

Table 2. Features of familial syndromes associated with pheochromocytoma [8, 9, 34, 49, 50, 57, 60, 164, 165]

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
<th>Inheritance</th>
<th>Clinical features</th>
<th>Age at presentation (yrs)</th>
<th>Frequency of mutation</th>
<th>Penetrance of disease</th>
<th>Frequency of malignant disease</th>
<th>Catecholamines</th>
<th>Common site of disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>VHL</td>
<td>VHL</td>
<td>Autosomal dominant</td>
<td>Renal cell cysts and carcinomas, Retinal and CNS hemangioblastomas, Endolympathic sac tumors, Epididymal cystadenomas, Pancreatic neoplasms and cysts, Pheochromocytomas</td>
<td>30 (range, 5–54)</td>
<td>2%–9%</td>
<td>7%–18%</td>
<td>&lt;10%</td>
<td>Noradrenaline-producing tumors only</td>
<td>Adrenal (predominates) and extra-adrenal abdominal and thoracic; often multifocal or bilateral adrenal disease</td>
</tr>
<tr>
<td>MEN type 2</td>
<td>RET</td>
<td>Autosomal dominant</td>
<td>Medullary thyroid carcinoma, Pheochromocytoma, Hyperparathyroidism, Cutaneous lichen amyloidosis</td>
<td>Type 2A 39.5 (range, 14–68)</td>
<td>3%–5%</td>
<td>50%</td>
<td>&lt;5%</td>
<td>Epinephrine-producing tumors predominate</td>
<td>Adrenal; bilateral disease common, extra-adrenal disease rare</td>
</tr>
<tr>
<td>MEN type 2</td>
<td>RET</td>
<td>Autosomal dominant</td>
<td>Medullary thyroid carcinoma, Pheochromocytoma, Multiple neurofibromas, Marfanoid habitus</td>
<td>Type 2B 32.4 (range, 15–41)</td>
<td>50%</td>
<td>60%</td>
<td>5%</td>
<td>Epinephrine-producing tumors predominate</td>
<td>Adrenal; bilateral disease common, extra-adrenal disease rare</td>
</tr>
<tr>
<td>NF1</td>
<td>NF1</td>
<td>Autosomal dominant</td>
<td>Multiple neurofibromas, Café-au-lait skin spots, Pheochromocytomas</td>
<td>40 (range, 25–69)</td>
<td>2%–4%</td>
<td>0.1%–5.5%</td>
<td>&lt;10%</td>
<td>Both noradrenaline and epinephrine</td>
<td>Adrenal; bilateral disease common, extra-adrenal disease rare</td>
</tr>
<tr>
<td>PGL4</td>
<td>SDHB</td>
<td>Autosomal dominant</td>
<td>No clinical phenotypic features, Pheochromocytoma/paraganglioma</td>
<td>34 (range, 10–58)</td>
<td>2%–7%</td>
<td>50% by 31 yrs</td>
<td>77% by 50 yrs</td>
<td>Noradrenaline-producing tumors predominate</td>
<td>Extra-adrenal (generally solitary) abdominal and thoracic pheochromocytoma predominates; if adrenal then commonly bilateral disease</td>
</tr>
<tr>
<td>PGL1</td>
<td>SDHD</td>
<td>Maternal imprinting</td>
<td>No clinical phenotypic features, Paraganglioma/pheochromocytoma</td>
<td>31.2 (range, 17–59)</td>
<td>3%–5%</td>
<td>50% by 31 yrs</td>
<td>80% by 50 yrs</td>
<td>Noradrenaline-producing tumors predominate</td>
<td>Head and neck paragangliomas predominate (gliomas tumors); if adrenal then commonly bilateral disease; often multifocal disease</td>
</tr>
<tr>
<td>PGL3</td>
<td>SDHC</td>
<td>Autosomal dominant</td>
<td>No clinical phenotypic features, Head and neck paraganglioma</td>
<td>46 (range, 13–73)</td>
<td>&lt;0.1%</td>
<td>Unknown</td>
<td>Uncertain (≤5%)</td>
<td>Nonfunctioning</td>
<td>Head and neck paragangliomas</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, central nervous system; MEN, multiple endocrine neoplasia; NF1, neurofibromatosis type 1; PGL, pheochromocytoma/paraganglioma syndrome; VHL, von Hippel-Lindau.
Table 3. Pheochromocytoma of the adrenal gland scaled score (PASS)

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular invasion</td>
<td>1</td>
</tr>
<tr>
<td>Capsular invasion</td>
<td>1</td>
</tr>
<tr>
<td>Periadrenal adipose tissue invasion</td>
<td>2</td>
</tr>
<tr>
<td>Large nests or diffuse growth</td>
<td>2</td>
</tr>
<tr>
<td>Focal or confluent necrosis</td>
<td>2</td>
</tr>
<tr>
<td>High cellularity</td>
<td>2</td>
</tr>
<tr>
<td>Tumor cell spindling</td>
<td>2</td>
</tr>
<tr>
<td>Cellular mononcy</td>
<td>2</td>
</tr>
<tr>
<td>Increased mitotic figures (&gt;3 per 10 high-power fields)</td>
<td>2</td>
</tr>
<tr>
<td>Atypical mitotic figures</td>
<td>2</td>
</tr>
<tr>
<td>Profound nuclear pleomorphism</td>
<td>1</td>
</tr>
<tr>
<td>Hyperchromasia</td>
<td>1</td>
</tr>
</tbody>
</table>

Histological criteria are each given a score. The sum of the scores groups adrenal pheochromocytomas into those with potential for biologically aggressive behavior (PASS ≥4) and those likely to behave in a benign fashion (PASS <4).

**VHL Syndrome**

VHL syndrome is characterized by the development of retinal and central nervous system (CNS) hemangioblastomas, clear cell renal cell carcinoma, pheochromocytoma, pancreatic and renal cysts, endolymphatic sac tumors, and papillary cystadenoma of the epididymis or broad ligament [35–38]. *VHL* germline mutations are inherited in an autosomal dominant manner. Ninety percent of gene carriers will express one or more of the clinical manifestations of the syndrome by 60 years of age [39] and 7%–18% will develop pheochromocytomas at a mean age of 30 years (range, 5–54) [8, 40–42]. From 3% to 11% of patients presenting with an apparently sporadic pheochromocytoma will have a VHL germline mutation [8, 43, 44]. VHL-associated pheochromocytomas frequently occur as synchronous or metachronous bilateral adrenal lesions but can also be extra-adrenal in location, and frequently secrete norepinephrine but generally do not produce epinephrine [41, 45]. Long-term morbidity and mortality are usually related to complications from retinal and CNS hemangioblastomas and metastatic renal cell carcinoma [36–38].

**MEN-2**

Activating germline mutations of the *RET* proto-oncogene result in MEN-2. Medullary thyroid carcinoma (MTC) is the most common presenting feature of MEN-2, with a penetrance of >90% by 50 years of age [46, 47]. Pheochromocytoma occurs in approximately 50% of patients with MEN-2 [48]. In 9%–27% of MEN-2 patients, pheochromocytoma is the first manifestation of the syndrome; of these patients, 35%–73% will have MTC diagnosed concurrently [48–50]. The mean age of presentation of pheochromocytoma is 39.5 years (range, 14–68) for MEN-2A and 32.4 years (range, 15–41) for MEN-2B [49]. Extra-adrenal disease is rarely seen with MEN-2 [49]. Adrenal pheochromocytoma can present as either unilateral or bilateral disease. Of those initially presenting with unilateral disease, 50% will develop a pheochromocytoma in the contralateral gland over a period of 8–10 years [48]. MEN-2-associated pheochromocytomas generally secrete epinephrine, in contrast to VHL-associated tumors [45].

**NF1**

The diagnosis of NF1 is usually made on the following clinical criteria: greater than six café-au-lait spots, more than two neurofibromas, and axillary freckling [51]. NF1 is associated with a greater incidence of a variety of neuroendocrine tumors, including pheochromocytomas [52, 53], but the occurrence of pheochromocytoma is relatively uncommon, with an estimated lifetime incidence of 0.1%–5.5% [54].

**Familial Pheochromocytoma/Paraganglioma Syndromes**

Recently described germline mutations in *SDHB*, *SDHD*, and *SDHC* (previously PGL4, PGL1, and PGL3) result in familial pheochromocytoma and/or paraganglioma. *SDHB* mutations appear to be the most common, with an overall frequency of 1.7%–6.7% in patients presenting with pheochromocytoma [55]. Patients with *SDHB* mutations predominately develop extra-adrenal pheochromocytoma and are at high risk for malignant disease [56]. Head and neck paragangliomas predominate in *SDHD* mutation carriers; however, they are more likely than *SDHB* carriers to have multifocal disease and less likely to be malignant. Importantly, both tumor types (pheochromocytoma or head and neck paraganglioma) may develop in *SDHB* or *SDHD* mutation carriers, which must be considered with the long-term monitoring of disease in these patients [57].

*SDHD* mutations are maternally imprinted; therefore, carriers who inherit the mutation from their mother remain disease free but their offspring are at risk of inheriting the mutation [31]. *SDHC*-associated disease is rare and was thought to occur exclusively as head and neck paragangliomas; however, an *SDHC*-associated extra-adrenal abdominal pheochromocytoma was recently reported [58]. Malignant pheochromocytoma/paraganglioma appears to be uncommon in *SDHD-* and *SDHC*-associated disease [59–61].
DIAGNOSIS AND EVALUATION

Much has been written about the diagnostic evaluation of pheochromocytoma. Useful decision algorithms have been proposed for a suspected pheochromocytoma [13], adrenal incidentaloma [26, 62], and patients with a history of malignancy [27]. As a general rule, pheochromocytomas are first established by a sensitive biochemical diagnosis and then confirmed by specific imaging studies. For the adrenal incidentaloma already discovered by computed tomography (CT) or magnetic resonance imaging (MRI), a bio-

**Figure 1.** Flowchart of diagnosis and management of pheochromocytoma. Abbreviations: CT, computed tomography; MIBG, metaiodobenzylguanadine; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.
chemical diagnosis should be established before more specific imaging studies are done. A flowchart of our strategy for management and diagnosis is found in Figure 1.

**Biochemical Evaluation**

Historically, many institutions relied upon 24-hour measurements of total urinary catecholamines and metanephrines. In studies from the Mayo Clinic, urinary measurements of total catecholamines and metanephrines were found to have a sensitivity and specificity of 98% and 98%, respectively [63, 64]. If a urinary collection is done, it is advisable to measure twice to account for the episodic nature of pheochromocytoma. Although urinary dopamine has a specificity of 99%, it is a poor first choice because of a sensitivity of 63%. Elevations in either urinary norepinephrine or epinephrine were found to have a sensitivity of 100% and a specificity of 97% [65]. Unfortunately, the 24-hour collection method can place an undue burden on the patient. Tricyclic antidepressants can cause a false-positive result with the measurement of urinary catecholamines [66].

The measurement of plasma metanephrines is extremely sensitive, and some have advocated its use as a first-line test. Its sensitivity is nearly 99%, and its specificity has been reported to be in the range of 85%–89% [64, 67, 68]. Because of its high negative-predictive value and quick results, many argue that a negative result is sufficient to exclude pheochromocytoma [68]. Some causes of false-positive results include tricyclic antidepressants, phenoxybenzamine, radiographic contrast dye, congestive heart failure, major depression, and panic disorder [11, 14, 15]. The clonidine suppression test can be useful to distinguish false-positive results from true-positive results. The centrally acting α2 agonist is unable to suppress the secretion of epinephrine and norepinephrine in pheochromocytoma, and it has a reported diagnostic accuracy of 92% [69, 70]. This may not be valid for patients with normal catecholamine levels: one group found that the clonidine suppression test has a false-positive rate five times higher than that in those with elevated catecholamines [71]. However, we do not recommend its use because of the reliability and ease of use of other tests. We recommend evaluation of fractionated plasma metanephrines as the first test in cases of suspected pheochromocytoma: it is easy and reliable and effectively rules out pheochromocytoma.

Historical tests worth mentioning include the glucagon stimulation test, chromogranin A, and direct measurements of plasma catecholamines. The glucagon stimulation test is infrequently used because it does not reliably increase hormonal secretion [72, 73]. Although the overlap with carcinoid tumors and adrenal cortical carcinoma lowers its specificity, serum chromogranin A levels were found to be elevated in 86% of patients with pheochromocytoma [74–76]. While not directly useful in diagnosis, chromogranin A levels are useful in the management of malignant pheochromocytoma as a marker of tumor burden and progression of disease. Ultimately, the combination of different biochemical investigations does not increase diagnostic accuracy, and measurement of plasma free metanephrines is the preferred test in patients with both hereditary and sporadic disease [67].

**Imaging**

Imaging tests should be employed for localization after a biochemical diagnosis is confirmed [77]. With the exception of the smaller tumors seen in hereditary disease, CT and MRI are sensitive enough to localize most pheochromocytomas [78]. Ninety-five percent of extra-adrenal pheochromocytomas are found in the abdomen and pelvis [79]. Both CT and MRI have a sensitivity of 98%–100% for adrenal pheochromocytomas [80], but MRI is more sensitive (94% versus 90%) for extra-adrenal pheochromocytomas [17, 81, 82]. Unfortunately, these tests have a specificity of approximately 70% because of the high incidence of adrenal incidentalomas [83].

If a solitary tumor is localized, confirmatory studies may be pursued but are not essential if there is no suggestion of familial disease. The most commonly used studies are either iodine-123–labeled metaiodobenzylguanadine (123I-MIBG) or 131I-MIBG scintigraphy, which use a norepinephrine precursor compound to localize the hypersecretory adrenergic tissue. When a pheochromocytoma is confirmed both biochemically and by CT or MRI, scintigraphy has been shown to be unnecessary for benign sporadic or familial pheochromocytoma [84, 85]. 123I-MIBG is superior to 131I-MIBG scintigraphy for the evaluation of metastases, but it is not widely available [86]. Both have a specificity of approximately 95%, but the sensitivity of 123I-MIBG is higher (90% versus 77%) [87]. Moreover, 123I-MIBG can be used to perform single photon emission CT. The absence of β-emission and a shorter half-life result in a 20 times greater initial level of radioactivity administered to the patient without increasing the absorbed radiation dose, which accounts for the greater sensitivity of 123I-MIBG [88]. In centers where this is not available, however, 131I-MIBG can still be used successfully. In contrast to benign tumors, MIBG does have a role in the staging and diagnosis of malignant disease, where it can be used to find metastases too small to be detected by CT or MRI [89].

Another important imaging technique is positron emission tomography (PET). Several different agents have been used for localization of pheochromocytoma. The more sen-
sitive agents include $^{18}$F-fluorodeoxyglucose [90] and $^{82}$rubidium [91], while more specific agents incorporate $^{11}$C-hydroxyephedrine [92] and $^{6,18}$F-fluorodopamine [87]. While studies have shown remarkably high sensitivity and specificity, the series are small and many of the agents are not yet in widespread clinical use. Generally considered to be superior to MIBG scintigraphy, PET may one day play a major role in the imaging of metastatic pheochromocytoma because of its ability to specifically localize small tumors distributed throughout the body [87, 93, 94].

In conclusion, our recommendation is to first attempt to localize the tumor by CT or MRI. Routine preoperative imaging with MIBG in patients with well-localized tumors is probably unnecessary, but may be beneficial in patients with bilateral lesions or a clinical suspicion of malignancy. If the tumor cannot be found and pheochromocytoma is still strongly suspected, further imaging with MIBG is an appropriate measure. There are excellent decision trees available for the appropriate approach to imaging [13, 95].

**TREATMENT OF PHEOCHROMOCYTOMA**

**Preoperative Management**

Once the diagnosis of a pheochromocytoma is made, appropriate preoperative medical management is necessary to reduce the risk for perioperative complications. During surgical manipulation of the tumor, massive catecholamine release may occur, which can exceed the normal plasma concentration by $>1,000$ times. This can result in hypertensive crisis, cardiac arrhythmias, cerebral vascular accident, myocardial infarction or ischemia, pulmonary edema, and multiorgan failure [96]. The introduction of pharmacological pretreatment in the 1950s reduced the perioperative mortality rate from as high as 45% to <2% [74–76, 97, 98].

The aim of pharmacological management is to abolish or reduce the potentially lethal swings in blood pressure that can occur during induction of an anesthetic and surgical manipulation of the tumor, and to prevent the severe hypotension that can result immediately following removal of the tumor. Stabilization of blood pressure is achieved by the use of a single antihypertensive agent or a combination of antihypertensive agents preoperatively and intraoperatively to counteract excessive catecholamine adrenergic activity, volume expansion with i.v. fluid to prevent hypotension once maximal vasodilatation is achieved, and inotropic support after excision of the pheochromocytoma if required [99]. There are currently no randomized prospective trials to establish the optimal preoperative pharmacological management of pheochromocytoma. As a result, there is no clear consensus regarding the drug of choice [100]. $\alpha$-adrenoceptor antagonists, dihydropyridine calcium channel receptor blockers, the tyrosine hydroxylase inhibitor $\alpha$-methyltyrosine, and the competitive $\alpha$- and $\beta$-receptor blocking drug labetalol have all been successfully used in an oral form for the preoperative treatment of pheochromocytoma [84, 85, 101–104]. The drug dosage is generally reassessed and titrated every 2–3 days until the expected therapeutic response is achieved. Adequate dosage is indicated by a reduction in blood pressure to normal levels with mild orthostatic hypotension (not less than 80/45 mmHg). Treatment is usually commenced 10–14 days preoperatively to allow adequate time for blood pressure normalization and volume expansion to occur. Intravenous saline is administered if further volume expansion is required prior to surgery [76, 105].

The two most commonly used $\alpha$-adrenergic antagonists are phenoxybenzamine and doxazosin [34]. Phenoxybenzamine is a nonselective, noncompetitive $\alpha$-adrenergic antagonist with a plasma half-life of 24 hours. Starting dosages of 20–40 mg daily are titrated depending on patient response. Nonselective $\alpha$-adrenergic blockade can result in reflex tachycardia, for which the addition of a $\beta$-adrenergic blocker is often required for symptomatic relief from tachycardia or tachyarrhythmias. $\beta$-adrenergic blockers should never be used alone and should be commenced only after adequate pretreatment with $\alpha$-adrenergic blockade, because unopposed $\alpha$-adrenergic receptor stimulation can induce a catastrophic hypertensive crisis [76, 100, 105]. Labetalol has both $\alpha$- and $\beta$-receptor antagonist activity, is available in oral and i.v. preparations, and has been successfully used for the perioperative control of blood pressure in pheochromocytoma patients and in patients with metastatic disease; however, patient response may be variable [104, 106, 107]. Doxazosin is a selective $\alpha_1$-adrenergic antagonist and therefore does not result in tachycardia; however, as a competitive antagonist it can be displaced by high levels of endogenous catecholamines [108]. It has a plasma half-life of 20 hours and is usually given in increasing doses from 1 mg to 16 mg once a day [109]. Other selective $\alpha_1$-adrenergic antagonists include prazosin and terazosin, which have shorter half-lives and therefore require more frequent administration [100].

The dihydropyridine calcium channel blockers are useful in patients who are normotensive but have paroxysmal episodes of hypertension, because they are less likely to cause significant orthostatic hypotension or overshoot hypotension. Reduction in arterial blood pressure results from inhibition of norepinephrine-mediated transmembrane calcium influx in vascular smooth muscle [110]. Dihydropyridine calcium channel blockers do not induce tachycardia and may also reduce catecholamine-associated coronary artery spasm, and are therefore particularly useful in pheo-
chromocytoma patients with coronary vasospasm or myocarditis [100, 105, 109]. Amlodipine is given in a dose of 10–20 mg/day, nifedipine is given at 30–90 mg/day, nicardipine is given at 60–90 mg/day, and verapamil is given at 180–540 mg/day [105]. Nicardipine infusion has also been used effectively for the rapid control of hemodynamic changes intraoperatively [109, 111].

α-methylyrosine competes competitively with tyrosine hydroxylase, which catalyzes the conversion of tyrosine to dihydroxyphenylalanine, the first step of catecholamine synthesis [76, 105, 112]. It is centrally acting and therefore can result in sedation, anxiety, psychic disturbance, and extrapyramidal side effects that may be exacerbated by the concurrent use of a dopamine antagonist. Patients may also experience severe diarrhea necessitating treatment with antidiarrheal agents. In patients with pheochromocytoma, a dose of 1–4 g/day of α-methylyrosine is administered and the maximum biochemical effect is observed within 2–3 days. Response to treatment can be observed by clinical response and measured by a reduction in urinary or plasma catecholamine levels, and the drug dose can be titrated accordingly, thereby reducing the frequency and severity of the side effects that may occur [113, 114]. α-methylyrosine is effective for the management of patients with extensive metastatic pheochromocytoma; however, it can also be used for preoperative preparation of pheochromocytoma patients. It may therefore be a useful alternative for patients in whom α-adrenoceptor or calcium channel blockers are contraindicated [76, 100, 105].

Adequate preoperative medical preparation limits intraoperative cardiovascular instability; however, hypertensive crisis can still occur as a result of significant catecholamine release that can occur with surgical manipulation of the tumor. Volume expansion should be optimized preoperatively by the administration of i.v. saline or colloid, because this minimizes the blood pressure fluctuations that can occur intraoperatively with the administration of antihypertensive agents. Pharmacological agents that can be used to control blood pressure intraoperatively include phentolamine, sodium nitroprusside, nitroglycerine, magnesium sulfate, and urapidil. Cardiac tachyarrhythmias can be treated with short-acting β-blockers, such as esmolol or labetalol [76, 100, 102].

Operative Approach
Whenever possible, pheochromocytomas should be removed using a laparoscopic approach, because this technique results in less postoperative pain, a shorter hospital stay, quicker recovery, and better cosmesis when compared with an open surgical approach. Open procedures are reserved for very large tumors or extra-adrenal tumors in locations difficult to remove laparoscopically. A transperitoneal or retroperitoneal approach can be used depending on the site of the tumor and surgeon preference and experience [100, 115–118]. Removal of benign solitary tumors results in biochemical cure if complete excision is achieved; however, the long-term recurrence rates of pheochromocytoma are reported to be in the range of 0%–17% of patients [9, 98, 119]. Unlike adrenocortical tumors, in adrenal pheochromocytomas with local disease only, size is a poor predictor of malignancy and should therefore not be the deciding factor when considering a laparoscopic resection, because adrenal pheochromocytomas ≥10 cm can be safely removed with a laparoscopic approach [116, 117]. Regardless of tumor size, laparoscopic resection for pheochromocytoma should be converted to an open procedure for a difficult dissection, uncontrolled bleeding, suspicion of malignancy, or surgeon inexperience [116, 120, 121].

Bilateral cortical-sparing adrenalectomy has been advocated for patients presenting with bilateral adrenal pheochromocytoma or for MEN-2 and VHL patients presenting with unilateral adrenal pheochromocytoma, because of the high incidence of synchronous and metachronous disease that occurs in these familial pheochromocytoma syndromes [34, 122]. In expert hands, approximately 65% of patients remain corticosteroid independent, with a long-term recurrence rate from the adrenal remnant of 10%–20% [122–124].

Postoperative Management
Patients may require monitoring in a high-dependency unit or intensive care setting for the first 12–48 hours because cardiovascular and metabolic instability can occur. Blood pressure and volume should be monitored using invasive arterial pressure and central venous pressure monitoring. Postoperative hypotension can result from the persisting action of antihypertensive agents used in the pre- and postoperative phases of management [100], as well as adrenoreceptor downregulation resulting from chronic high levels of circulating catecholamines [125]. Norepinephrine may be required to maintain blood pressure in the early postoperative period. Hypoglycemia can occur postoperatively and should be monitored for and corrected [126].

Biochemical testing should be performed postoperatively to confirm the absence of any residual disease; however, normal biochemical tests do not exclude the presence of microscopic disease [127]. Patients with familial pheochromocytoma should undergo life-long annual clinical and biochemical assessment because of the high risk for recurrent disease as well as screening for other syndromic neoplasms. Patients with sporadic pheochromocytoma should also be followed up indefinitely, because there are
currently no reliable tests to discriminate benign from malignant disease, and recurrence rates up to 17% have been reported even in expert hands [9, 100].

MALIGNANT DISEASE
The World Health Organization tumor definition of a malignant pheochromocytoma is the presence of metastases [128], but this distinction between benign and malignant pheochromocytoma does not account for recurrent or locally invasive tumors. Frequently the diagnosis of malignant disease can only be made retrospectively once metastases have become evident. Metastases occur most frequently to bone, liver, and lungs and can appear as many as 20 years after initial presentation [127]. Currently, there are no prognostic tests that can reliably predict which patients are at risk of developing metastatic disease.

Histopathological and Molecular Markers of Malignant Disease
As with many other neuroendocrine tumors, a pathologist cannot determine whether a tumor is benign or malignant based on histological features alone (Table 3, [166]). The diagnosis of a malignant pheochromocytoma is often only made in retrospect once metastasis has occurred [128, 129]. In pheochromocytomas without local invasion, as opposed to adrenocortical tumors, size is not a predictive factor for malignancy [116].

The histological scaling system Pheochromocytoma of the Adrenal Gland Scaled Score uses a range of histological criteria to group adrenal pheochromocytomas into those with potential for biologically aggressive behavior (atypical) and those likely to behave in a benign fashion; however, it cannot predict malignancy within the atypical pheochromocytoma group. The immunohistochemical markers Ki-67, p53, MIB-1, inhibin/activin β-subunit, heat shock protein-90 (HSP-90), cyclo-oxygenase, N-cadherin, vascular endothelial growth factor, endothelin receptor type A and B, EM66, and several neuroendocrine- and catecholamine-related markers such as chromogranin A, neuropeptide Y, and 3,4-dihydroxyphenylalanine may be indicative of malignant disease; however, none has been shown to be a reliable prognostic marker [130–132].

The genetic changes that induce malignant disease remain unclear. Certain groups are predisposed to malignant disease. For example, patients with SDHB mutations are more likely to develop malignant disease [56, 59, 133] and nondiploid tumors have also been found to be associated with malignancy [134]. Gene expression and protein profiling are beginning to identify the genetic characteristics of malignant pheochromocytomas [135]. A recent gene-expression profiling study comparing nine benign and nine malignant pheochromocytomas identified approximately 100 genes demonstrating a statistically significant differential expression [136]. A low molecular weight (LMW) protein profile study generated from the serum of 33 patients with benign pheochromocytoma and 34 patients with malignant pheochromocytoma was able to identify combinations of LMW molecules that could distinguish all metastatic from benign pheochromocytoma patient serum samples [130]. These studies demonstrate the potential of profiling studies to discriminate between benign and malignant pheochromocytomas; however, validation of these results is required in larger case series.

MANAGEMENT OF MALIGNANT DISEASE
Once an individual has developed metastatic disease, the overall survival rate is 50% at 5 years. Whereas survival has exceeded 30 years in some patients, treatments for malignant disease are generally poor. Morbidity and mortality are often related to tumor burden because of high circulating catecholamines and the mass effect of metastases [80, 137, 138]. Malignant pheochromocytomas are generally resistant to chemotherapy and radiotherapy, and patients therefore have a poor prognosis, with treatment aimed at palliative control of symptoms [139, 140].

Principles of management with malignant pheochromocytoma include pharmacologic control of symptoms and tumor mass reduction followed by radionuclide therapy with or without chemotherapy. Tumor mass reduction is achieved by surgical resection of the primary tumor and local or distal metastases [141, 142]. Hepatic resection should be considered for localized liver metastases; however, less invasive techniques such as arterial embolization or chemembolization, cryoablation, and radiofrequency ablation will provide transient responses [143, 144]. Widespread liver metastases may respond to trans-catheter arterial embolization with minimal morbidity [145].

131I-MIBG is an analogue of norepinephrine, which is sequestered in neurosecretory granules of chromaffin cells. Treatment with high-dose 131I-MIBG results in an objective tumor response in 30% of patients, stabilization of disease in 57% of patients, and progression of disease in 13% of patients. A reduction in catecholamine secretion is seen in up to 45% of patients [146]. The radiolabeled somatostatin analogues 111In-pentetreotide/111In-DOTA-octreotide, 90Y-DOTA-octreotide, 177Lu-DOTA-octreotide, and 90Y-DOTA-Lanreotide have also been used with a similar tumor response in patients with tumors demonstrating uptake of the somatostatin radionuclide [147, 148].

Chemotherapy may be used in combination with radionuclide therapy, particularly when there is extensive residual disease or poor uptake and response to radionuclide
treatment. Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) is well described, with transient tumor response and symptomatic improvement in up to 65% of cases [149, 150]. Treatment regimes with etoposide and cisplatin [151], an anthracycline plus CVD [152], and the cytokine arabinoside [153] have also been used with similar response rates.

As molecular-profiling studies uncover the genetic changes that occur with tumorigenesis in pheochromocytoma, targeted gene therapy may soon become a treatment option. Recently, a phase II study evaluated the efficacy of temozolomide and thalidomide as a novel antineoplastic therapy for patients with malignant pheochromocytomas. Although a biochemical response of 40% and radiological response of 33% were achieved, significant lymphopenia occurred in a large number of patients, with opportunistic infections occurring in 10% [154]. More specific targeted therapy with imatinib mesylate [155] and everolimus [131] has been tried in a small number of patients with malignant pheochromocytomas; however, no significant effect was observed. Overexpression of the protein HSP-90 in malignant pheochromocytoma makes this a target of interest. HSP90 controls signaling pathways for proliferation/cell cycle control. The inhibitor of this protein 17-al-lylamino, 17-demethoxygeldanamycin has been shown to reduce cell proliferation in vitro; however, it has not yet reached clinical trials [156]. It is likely that, in the future, targeted gene therapy will be individualized based on the tumor molecular expression profile but also used in conjunction with current conventional treatments.

Surveillance and response to treatment can be assessed by the subjective relief of symptoms, control of hypertension, measurement of catecholamine levels, and radiological imaging with CT, MRI, MIBG, or PET. Although MIBG has a specificity of 95% and sensitivity of 77%–90%, it has a much lower detection rate for malignant pheochromocytomas (57%), and individual patients with malignant disease can have both MIBG-negative and MIBG-positive lesions [87].

**GENETIC TESTING**

The identification of a germline mutation is a crucial part of the management of pheochromocytoma. The detection of a germline mutation should prompt screening for multifocal pheochromocytomas and other syndrome-associated tumors and the offer of genetic testing to first-degree relatives. The presence of a germline mutation is ideally known prior to embarking on surgical management; however, in most centers, this is not feasible with the current scope of genetic testing. General guidelines from the First International Pheochromocytoma Symposium (2006) for considering genetic testing include any patient with any of the following criteria: suggestive family history; age <35 years; and multifocal, bilateral adrenal, extra-adrenal, or malignant disease [157]. Since the discovery and description of the SDH gene mutations, several studies have shown that the overall rate of germline mutation carriers in patients presenting with apparently sporadic pheochromocytoma may be as high as 24% [8, 9]. It has therefore been suggested that all patients with pheochromocytoma should be considered for genetic testing [55, 158]. The clinical picture of the patient, family history, and characteristics of the tumor will help guide the clinician to determine the most likely gene mutation (VHL, SDHB, SDHD, RET) and hence prioritize the order in which gene testing should be performed (Table 2).

**FUTURE DIRECTIONS**

Much attention has recently been devoted to pheochromocytoma as the understanding of this disease continues to improve. Serum tests have achieved a high sensitivity and specificity, and new imaging techniques continue to develop. 123I-MIBG is superior to 131I-MIBG scintigraphy for the evaluation of metastases, but the availability of this scanning modality is not yet widespread in the U.S. While expensive, 6-18F-fluorodopamine PET is a selective and sensitive system that reliably locates both primary tumors and metastases. If it becomes widely available, it would greatly aid in the staging and management of malignant disease. Continually improving detection methods, especially screening of high-risk populations, will only contribute to the treatment and knowledge of these conditions in the future.

It has become clear that many apparently sporadic pheochromocytomas have a genetic component. Not only has there been a great deal of attention directed toward the hereditary components, but better predictive molecular factors have been identified for malignant pheochromocytoma, which could lead to more effective genetic testing [56]. In addition, microarray studies have identified a set of genes preferentially expressed in malignant pheochromocytoma [135]. Others have noted the growing usefulness of pheochromocytoma as a model for understanding cancer biology [159]. The combination of an identifiable hereditary component along with an understanding of the genetic and molecular defects in sporadic pheochromocytoma makes this a promising model and approach for insights into other cancers.

While treatment for benign pheochromocytoma remains surgical resection, therapy for malignant disease is
unsatisfying at best. Combination therapy with $^{131}$I-MIBG and chemotherapy using cyclophosphamide, dacarbazine, and vincristine produced additive effects, but there was not a significant long-lasting benefit [160]. Radiofrequency ablation of hepatic and bony metastases has shown symptomatic relief in some patients [144]. Current studies focus on targeted pharmacologic interventions of specific pathways within pheochromocytoma cells, specifically Raf-1 [161], glycogen synthase kinase-3β [162], and Notch-1 [163]. These pathways are currently being targeted in clinical trials for carcinoids and medullary thyroid cancer, and future experiments will be directed toward clinical applications of these treatments. With a better understanding of the molecular mechanisms of these tumors, better treatments could become possible. The future is wide open for improvements in the understanding and treatment of this disease.

**AUTHOR CONTRIBUTIONS**

**Conception/design:** Joel T. Adler, Goswin Y. Meyer-Rochow, Herbert Chen, Diana E. Benn, Bruce G. Robinson, Rebecca Sippel, Stan B. Sidhu

**Financial support:** Herbert Chen, Stan B. Sidhu

**Administrative support:** Herbert Chen, Stan B. Sidhu

**Manuscript writing:** Joel T. Adler, Goswin Y. Meyer-Rochow, Herbert Chen, Diana E. Benn, Bruce G. Robinson, Rebecca Sippel, Stan B. Sidhu

**Final approval of manuscript:** Joel T. Adler, Goswin Y. Meyer-Rochow, Herbert Chen, Diana E. Benn, Bruce G. Robinson, Rebecca Sippel, Stan B. Sidhu

**REFERENCES**


31. Baysal BE, Ferrell RE, Willett-Brozick JE et al. Mutations in SDHD, a


