Pheochromocytoma: An Update on Risk Groups, Diagnosis, and Management

Mary Ann Nguyen-Martin, MD
Gary D. Hammer, MD, PhD

Pheochromocytomas are chromaffin cell tumors, usually originating in the adrenal medulla, that can secrete epinephrine (adrenaline), norepinephrine (noradrenaline), and/or dopamine. This tumor has been "likened to a pharmacologic bomb that may suddenly secrete massive amounts of catecholamines and cause marked elevations of blood pressure."[1] If these occasionally "silent bombs" are not quickly recognized and treated, they can lead to fatal cardiovascular disease. Therefore, the most crucial step in diagnosing a pheochromocytoma is to include it in the differential diagnosis.

In the past decade, there have been numerous advances in the biochemical diagnosis and localization techniques for pheochromocytomas. Furthermore, ongoing studies in antihypertensive treatment and modern surgical methods have transformed the therapeutic approach to these tumors. This article reviews the epidemiology, risk factors, clinical features, and advances in diagnosis and management of pheochromocytomas.

TAKE HOME POINTS

- The "rule of 10s" is an outdated axiom that can no longer be used as an epidemiologic guide to pheochromocytomas.
- Genetic testing should be performed in the following groups: patients with a family history of pheochromocytoma, patients with bilateral or multifocal tumors or malignant or extra-adrenal pheochromocytoma, and patients who are aged 50 years or younger when diagnosed with pheochromocytoma.
- Plasma free metanephrine levels are the biochemical test of choice for excluding pheochromocytomas.
- Computed tomography scanning and magnetic resonance imaging should be used as first-line imaging modalities for localizing pheochromocytomas.

EPIDEMIOLOGY

The "Rule of 10s"

Clinicians have conventionally been taught the "rule of 10s" as an epidemiologic guide to pheochromocytomas. The rule of 10s states that 10% of pheochromocytomas are extra-adrenal (of which 10% of these are extra-abdominal), 10% are malignant, 10% are bilateral, 10% are found in patients without hypertension, and 10% are familial. However, recent studies suggest that up to 98% of pheochromocytomas occur in the abdomen and pelvis, less than 2% occur in the chest, and 0.2% occur in the neck.[1] In addition, the incidence of malignant pheochromocytomas appears to be closer to between 13% and 26%.[2] Finally, in a cohort of 271 patients with sporadic pheochromocytoma and no family history of the disorder, 66 patients (24%) had germline mutations for 1 of 4 pheochromocytoma-susceptibility genes.[3] Although the rule of 10s has been an historic guideline, it appears that this axiom may be outdated.

Incidence

Pheochromocytomas can occur in patients of any age, and their incidence is similar in male and female patients. It is estimated that 1 to 8 (0.0001%–0.0008%) cases of pheochromocytoma occur per million persons annually; however, these tumors occur more frequently in certain populations.[4] First, the incidence of this disorder increases with advancing age, with the prevalence approaching 0.1% in elderly persons.[2] Second, the prevalence of pheochromocytoma is between 4% and 6.5% in patients who have an incidental adrenal tumor.[5] Third, the incidence of genetic predisposition to pheochromocytoma is between 10% and 20% in patients

Dr. Nguyen-Martin is a fellow, Division of Metabolism, Endocrinology, and Diabetes, and Dr. Hammer is an associate professor, Department of Internal Medicine; both are at the University of Michigan, Ann Arbor, MI.

Table 1. Most Common Hereditary Disorders Associated with Pheochromocytoma

Syndrome	Gene	Clinical Features
MEN2	RET	
Type A		Medullary thyroid carcinoma, primary hyperparathyroidism
Type B		Medullary thyroid carcinoma, ganglioneuromas, marfanoid habitus
VHL disease	VHL	
Type 2A		Hemangioblastoma, low risk of renal cell carcinoma
Type 2B		Hemangioblastoma, high risk of renal cell carcinoma
Type 2C		Pheochromocytoma only
NF1	NF1	Neurofibromas, café-au-lait spots, axillary or inguinal freckling, optic nerve glioma
PGL1/PGL4	SDHD/SDHB	Skull base tumors

Adapted from Elder EE, Elder G, Larsson C. Pheochromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. J Surg Oncol 2005;89:193–201; *and* Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol 2004;22:4991–5004.

MEN2 = multiple endocrine neoplasia II; NF1 = neurofibromatosis type 1; PGL = paraganglioma; SDHB = succinate dehydrogenase subunit B; SDHD = succinate dehydrogenase subunit D; VHL = von Hippel-Lindau.

diagnosed with an apparent pheochromocytoma.[3] Finally, this neuroendocrine tumor is found in up to 5% of patients evaluated for hypertension with suggestive clinical symptoms (eg, headache, diaphoresis, palpitations).[2]

Genetic Predisposition

All hereditary forms of pheochromocytoma are autosomal dominant and include multiple endocrine neoplasia type II (MEN2), von Hippel-Lindau (VHL) disease, von Recklinghausen's neurofibromatosis or neurofibromatosis type 1 (NF1), and the familial paraganglioma (PGL) syndromes 1 and 4. Tumors in MEN2 are the result of a mutation in the proto-oncogene RET. VHL disease is caused by the loss of the tumor suppressor gene VHL. Interestingly, pheochromocytomas are evident in VHL types 2A, 2B, and 2C but not in VHL type 1.[6] The NF1 tumor suppressor gene is responsible for tumor formation in neurofibromatosis. Finally, familial PGL1 and PGL4 are caused by mutations in SDHD (succinate dehydrogenase subunit D) and SDHB (succinate dehydrogenase subunit B), respectively. **Table 1** describes the features of the 4 most common hereditary disorders associated with pheochromocytoma. For nonsyndromic or sporadic pheochromocytoma, the overall likelihood that the patient has a germline mutation is variable: 5% for RET, 10% to 15% for VHL, 2% for NF1, and 1% to 4% for SDHD and SDHB.[6–8] However, early onset (age ≤ 35 years) or a family history of pheochromocytoma increase the likelihood that the patient has a mutation to 6.3% and 16.7%, respectively.[9]

Some clinical characteristics can help distinguish sporadic from germline pheochromocytomas. First, the occurrence of bilateral or multiple adrenal tumors suggests a germline mutation.[10] Second, patients with MEN2 or VHL disease (who usually exhibit abdominal pheochromocytoma) present at a younger age, with fewer symptoms, and milder hypertension than patients with nonhereditary pheochromocytoma.[10] One study showed that the mean age at diagnosis of pheochromocytoma for patients with VHL disease was 29.9 years versus 39.7 years for sporadic cases.[11] Although intra-abdominal pheochromocytoma can be found in NF1, this disease is always accompanied by other clinical features, such as neurofibromas and café-au-lait spots.[6] Last, PGL syndromes present as skull base tumors.[6] Therefore, the associated features for each of the hereditary disorders help distinguish between hereditary versus sporadic pheochromocytoma. Screening for genetic mutations is critically important when it can help identify patients who are at risk for developing multiple tumors.

Currently, genetic testing is recommended for patients with a family history of pheochromocytoma, patients with bilateral or multifocal tumors or malignant or extra-adrenal pheochromocytoma, and patients aged 50 years or younger when diagnosed with pheochromocytoma.[6,9]

CLINICAL FEATURES

Although it is a rare tumor, pheochromocytoma is often considered in many clinical scenarios given its myriad presentations. Symptoms become evident with massive catecholamine release, which can be induced by positional change (eg, standing, head-up tilt test), increased abdominal pressure, trauma, labor (in pregnant women), anesthesia, surgery, stress, exercise, drugs, or food.[12] For example, patients with a pheochromocytoma exhibit an average decrease of 14 mm Hg in systolic blood pressure during a head-up tilt test versus an average of 4 mm Hg in patients with essential hypertension.[13] The presentation of pheochromocytoma can range from normotensive and asymptomatic in patients with hereditary pheochromocytoma or small incidentalomas to potentially lethal symptoms in patients with larger, more functional, sporadic tumors.

Hypertension is paroxysmal in 48% of patients, persistent in 29%, and absent in 13%.[14] However, many patients exhibit 1 of the following signs and symptoms: hypertensive crisis, anxiety/panic attack, seizure, or essential hypertension unresponsive to conventional measures.[4] Clinical symptoms can occur intermittently on a daily basis or as infrequently as weekly or monthly. Individual episodes can last from a few minutes to many hours before gradually waning, leaving the patient fatigued.[1]

Characteristics that should signal a work-up for pheochromocytoma include hypertension refractory to multiple medications, wide swings in blood pressure, paradoxic response to antihypertensives (especially β-blockers), unexplained spells of dizziness, orthostatic hypotension in the absence of medication, a family history indicating risk for developing pheochromocytoma, or an incidental adrenal mass.[15,16] In addition to hypertension, the most common symptoms include headaches (80%) described as intense and global, palpitations (64%), and diaphoresis (57%).[13,17] Less typical presentations include tremor, anxiety, weakness, nausea, vomiting, flushing, chest or abdominal pain, constipation, ileus, and/or megacolon.[18] Moreover, up to 8% of patients with pheochromocytomas are completely asymptomatic, especially those with 1 of the 4 genetic syndromes associated with pheochromocytoma or patients with large cystic tumors.[17] The incidence of various symptoms in patients with pheochromocytoma is presented in **Table 2**.

Table 2. Incidence of Symptoms in 324 Patients Presenting with Pheochromocytoma

Symptom	Range (%)
Classic triad	
Headache	43–80
Palpitations	44–71
Diaphoresis	37–71
Less typical presentations	
Anxiety	15–72
Palpitations	44–71
Abdominal pain	14–62
Weakness	8–58
Chest pain	0–50
Hyperglycemia	> 50
Pallor	42–44
Nausea	10–42
Dyspnea	15–39
Tremor	13–38
Weight loss	7–23
Cholelithiasis	3–23
Flushing	4–19
Visual disturbance	11–22

Adapted from Ross EJ, Griffith DNW. The clinical presentation of pheochromocytoma. Q J Med 1989;71:485. By permission of Oxford University Press.

DIFFERENTIAL DIAGNOSIS

Severe paroxysmal hypertension (pseudopheochromocytoma) can manifest with symptoms similar to pheochromocytoma. Patients with this syndrome have only mildly elevated baseline blood pressures but present with hypertensive episodes marked by peak blood pressure greater than 200/110 mm Hg followed by periods of severe exhaustion.[19] Labile hypertension can also be mistaken for pheochromocytoma. Patients with labile hypertension report a definitive relationship between stress or emotional distress and elevated blood pressure, whereas patients with pheochromocytoma do not. Last, patients with panic disorder can present with psychiatric manifestations similar to the paroxysmal anxiety experienced with pheochromocytoma. However, a feeling of impending doom is the predominant feature in a true panic attack, with only mild elevations in blood pressure. In addition, the following conditions can cause a secondary elevation in plasma catecholamines: intracranial lesions, seizure, acute abdomen, eclampsia, shock, carcinoid syndrome, Guillain-Barré syndrome, hypoglycemia, myocardial ischemia, cerebrovascular accident, cocaine abuse, and severe congestive heart failure.[14,20] If there is a high pretest probability of pheochromocytoma (ie, hypertension in addition to headache, palpitation, or diaphoresis), then pheochromocytoma should be ruled out first before assessing for these other conditions.

DIAGNOSTIC EVALUATION

Biochemical Studies

The laboratory diagnosis of pheochromocytomas can be difficult because catecholamines are produced not only by the adrenal medulla but also by sympathetic nerves; therefore, high catecholamine levels are not specific to pheochromocytomas. In addition, the tumor may not produce adequate catecholamine amounts to induce the common signs and symptoms or elicit a positive biochemical result. Complicating the diagnosis, these neuroendocrine tumors secrete heterogeneous patterns of catecholamines and their metabolites; consequently, the simultaneous measurement of more than 1 analyte had been the traditional recommendation until recently.[16]

Current studies show that plasma free metanephrine

Table 3. Factors That Can Cause a False-Positive Diagnosis of Pheochromocytoma

Drugs
Acetaminophen
Tricyclic antidepressants
Antipsychotics
Levodopa
Ethanol
Clonidine withdrawal
Phenoxybenzamine
Diet
Caffeinated beverages
Decaffeinated beverages
Nicotine
Stressors
Myocardial infarction
Cerebrovascular accident
Cocaine abuse
Congestive heart failure class III/IV
Standing
Emotional stress

levels are the biochemical test of choice for excluding pheochromocytomas.[21,22] A plasma free metanephrine level less than 61 ng/L (0.31 nmol/L) excludes a pheochromocytoma, whereas a level above 236 ng/L (1.2 nmol/L) confirms the diagnosis; a value between 62 and 235 ng/L requires additional testing.[10] Metanephrine possesses the advantage of having a long plasma half-life when compared with the episodic nature of catecholamines released from normal and tumoral tissue. The sensitivity for plasma metanephrine is 97% in hereditary and 99% in sporadic cases. Furthermore, a large cohort study found that the median plasma metanephrine level was increased by sevenfold in hereditary and 21-fold in sporadic pheochromocytoma.[22] In this same study, the authors conclude that combining different tests does not improve the diagnostic yield beyond that of a single test of plasma free metanephrine levels. However, because the pretest probability of pheochromocytoma in patients with hypertension and provocative symptoms is only 0.5%,[10] and because these are rare tumors with low prevalence, the false-positive rate of free plasma metanephrine can exceed the true positive rate.

In a patient with positive plasma metanephrines, the posttest probability of pheochromocytoma varies among different risk groups: 3% in a patient with hypertension, 25% in a patient with an adrenal incidentaloma, and 82% in a patient with MEN2A.[16] The posttest probability of pheochromocytoma when the test is negative for the aforementioned groups is: 0.02%, 0.2%, and 2.7%, respectively.[16] Since the 24-hour urinary total metanephrines and catecholamines have a specificity up to 99% and yield fewer false-positive results, urine studies are a suitable alternative for ruling out pheochromocytoma. Although plasma metanephrines are superior for high-risk patients with a hereditary disposition, urinary measures may be preferred in those at low risk for pheochromocytoma.

Drugs, diet, and stressors can result in elevated plasma catecholamines, which can confound diagnostic studies (**Table 3**). Acetaminophen can interfere with plasma metanephrine assays; therefore, it should not be administered 5 days prior to biochemical testing. Other medications that may affect laboratory assays include tricyclic antidepressants and antipsychotics, levodopa, ethanol, withdrawal from clonidine, and phenoxybenzamine.[22,23] Both caffeinated and decaffeinated beverages contain the catechol caffeic acid, which interferes with assays of plasma catecholamines and metanephrines.[9] Nicotine can also affect results because it raises plasma catecholamine levels.[24] Finally, standing and emotional stress stimulate the release of catecholamines. To minimize these sources of false-positive catecholamine elevation, interfering medications should be stopped at least 2 weeks prior and blood samples should be drawn in the supine position after an overnight fast.

When the diagnosis is equivocal, more advanced testing may be required, usually under the guidance of an endocrinologist. Because the adrenal medulla is not the sole origin of norepinephrine, the clonidine suppression test is helpful in distinguishing between elevated norepinephrine levels secondary to sympathetic nerves versus true pheochromocytoma. Failure to suppress norepinephrine levels by at least 50% denotes a positive test (ie, pheochromocytoma).[10] Several factors can affect this test: false negatives can be caused by an intermittently secreting tumor, whereas false positives can be caused by diuretics or tricyclic antidepressants. The glucagon stimulation test is occasionally employed when plasma metanephrine levels are elevated but catecholamines are either normal or only moderately high. This highly specific test is positive (ie, pheochromocytoma) when there is at least a threefold increase in norepinephrine levels in response to glucagon.[10] However, this test can be fatal in patients with a pheochromocytoma because it can produce dangerous increases in blood pressure. Patients undergoing either test should be closely monitored for hypotension (clonidine suppression test) and

hypertension (glucagon stimulation test). The **Figure** depicts an algorithm for the biochemical tests pertinent to the work-up of pheochromocytoma.

Imaging and Localization Studies

Once biochemical confirmation is obtained, medical decision making must focus on tumor localization and medical management. Computed tomography (CT) scanning can detect adrenal pheochromocytomas between 0.5 and 1.0 cm in size. As most of these tumors are at least 3 cm, CT can detect adrenal pheochromocytomas with a sensitivity of 99%.[21] Unenhanced CT followed by contrast-enhanced and delayed contrast-enhanced CT imaging yields a sensitivity of 98% for adenomas as compared with other nonadenomatous tumors limited to the adrenal glands.[24,25] Most adrenal pheochromocytomas exhibit high attenuation (> 10 Hounsfield units [HU]) on unenhanced or enhanced CT scans as compared with lipid-rich adenomas. Occasionally, pheochromocytomas may undergo fatty change and exhibit a low attenuation similar to adenomas (< 10 HU) by CT and can also mimic adenomas' typical high contrast washout profile on delayed scans.[26]

Magnetic resonance imaging (MRI) also has excellent sensitivity, approaching 100%; however, the sensitivities for both CT and MRI decrease to below 91% when the tumor is extra-adrenal, metastatic, or recurrent.[27,28] MRI sensitivity drops to 85% when postoperative changes are evident.[29] Due to their dense capillary framework, pheochromocytomas appear bright with a high signal on T2 sequence. Although MRI is more costly than CT imaging, it has unique advantages. MRI can be used during pregnancy, allows more precise tissue characterization, and does not require intravenous contrast or ionizing radiation.[30] MRI has also been reported to provide superior assessment of the relationship between the tumor and its surrounding vessels and has the capability of imaging multiple planes, although modern multidetector CT can be reconstructed in multiple planes with higher resolution than MRI.[30]

The diagnostic priority in patients with a pheochromocytoma is to not only localize the primary tumor but also to discover possible metastatic lesions. Although CT and MRI provide localization and metastatic assessment, scintigraphy with metaiodobenzylguanidine (MIBG) is often employed to visualize extra-adrenal and recurrent tumors not detected by conventional measures. Although ^{131}I MIBG has a specificity of greater than 95%, it is not routinely used to diagnose pheochromocytoma because it only has a sensitivity of 77%.[27,31] ^{123}I MIBG improves sensitivity to almost 90% because it is particularly useful in detecting tumors

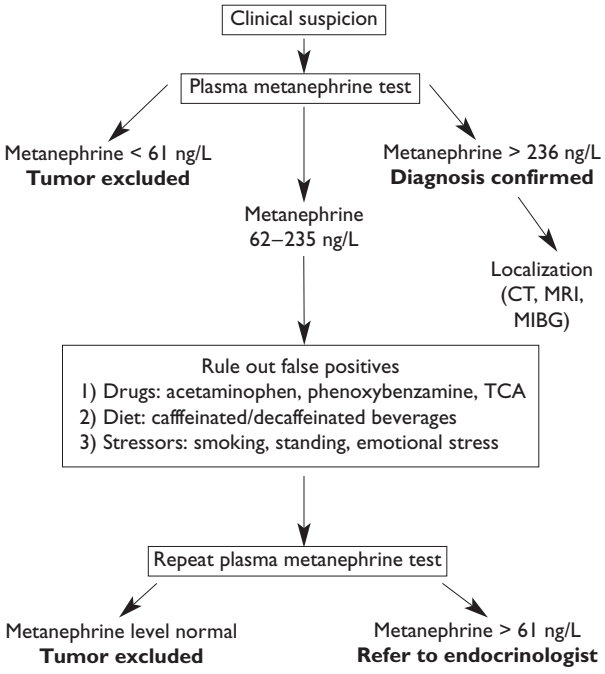

Figure. Algorithm for biochemical diagnosis of pheochromocytoma. CT = computed tomography; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging; TCA = tricyclic antidepressant.

with fibrosis or tumors in unusual locations or areas with distorted anatomy; however, it is only available at large academic institutions in the United States.[32–34] **Table 4** compares the different performance characteristics for CT, MRI, and MIBG.

An advanced imaging technique occasionally employed in difficult pheochromocytoma cases is positron emission tomography (PET) scanning. PET scans are primarily used to obtain information on the extent of metastatic disease. PET scan possesses several qualities that make it superior to MIBG: radiation risk is reduced, better temporal and spatial resolution is obtained, and pheochromocytoma can be detected within 2 to 5 minutes versus the 24 to 48 hours needed for MIBG.[35] Although additional imaging agents are available, including ^{11}C-hydroxyephedrine and 6-[^{18}F]Fluorodopamine, these modalities, including PET scans, are very expensive and commercially limited.

MALIGNANT PHEOCHROMOCYTOMA

Although the prevalence of malignancy in pheochromocytoma is often cited at 10%, it can be as high as 26%.[2] The detection of possible metastases is crucial because it can determine whether surgery, chemotherapy and/or radiation, or prolonged antihypertensive

Table 4. Statistical Values for Various Localization Techniques

	CT (%)	MRI (%)	MIBG (%)
Sensitivity	> 98*	100*	78†
Specificity	70	67	100
Positive predictive value	69	83	100
Negative predictive value	98	100	87

Data from Witteles RM, Kaplan EL, Roizen MF. Sensitivity of diagnostic and localization tests for pheochromocytoma in clinical practice. Arch Intern Med 2000;160:2521–4; Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 2004;89:479–91; *and* Ilias I, Yu J, Carrasquillo JA, et al. Superiority of 6-[^{18}F]-fluorodopamine positron emission tomography versus [^{131}I]-metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. J Clin Endocrinol Metab 2003;88:4083–7.

CT = computed tomography; MIBG = metaiodobenzylguanidine; MRI = magnetic resonance imaging.

*Sensitivities < 90% when tumor is extra-adrenal, metastatic, or recurrent or when postoperative changes are present.

†Value is for ^{131}I MIBG; sensitivity increases to almost 90% using ^{123}I MIBG.

therapy is required.[1] Malignancy is defined as "evidence of metastases at nonchromaffin sites distant from the primary tumor."[36] Distant metastases most commonly affect the lung, liver, and lymph nodes.[6] Currently, there is no histopathologic criteria to differentiate between benign versus malignant tumors other than routine indices, such as mitotic index and nuclear atypia. In addition, predicting which tumors will become malignant is difficult; however, large tumor size and local tumor extension at surgery greatly raise the suspicion.[14] The 5-year survival rate for malignant pheochromocytoma is variable, ranging from 36% to 74%.[2]

PREOPERATIVE MEDICAL MANAGEMENT

Most pheochromocytomas are benign, and surgical intervention can cure up to 90% of these tumors. Patient survival rates are approximately 98% to 100%.[10] Preoperative preparation is essential to avoid hypertensive crises that may be precipitated by intubation, anesthesia, or tumor manipulation upon removal. An α-adrenergic blocker must be given prior to administering a β-adrenergic blocker to avoid unopposed α action, which can lead to hypertensive crisis. Phenoxybenzamine (10–40 mg 4 times daily; maximum, 300 mg/d), an α-adrenergic blocker, is the common drug of choice; however, it has many disadvantages. It takes 2 to 3 weeks for intravascular volume expansion to occur (to assist in volume repletion, liberal salt intake is allowed), significant elevations in blood pressure can be seen during surgery, postoperative hypotension can occur if the α-blockade is too strong, and there is no evidence that α-blockade reduces perioperative mortality.[37,38] To avoid these disadvantages, selective α_1-blockers (eg, prazosin, terazosin, doxazosin) can be used because their shorter duration of action decreases the severity of postoperative hypotension and they do not cause reflex tachycardia.[14,37] After adequate α-blockade is achieved, β-blockers, such as propranolol (5–40 mg 4 times daily), can then be given to patients who continue to have tachycardia and arrhythmias. Adequate α-blockade is achieved once the patient's symptoms and blood pressure are controlled (blood pressure, < 160/90 mm Hg). Calcium channel blockers have also been used with some success and do not cause overshoot hypotension.[14] In more resistant cases, the combination of a calcium channel blocker and an α_1-blocker can provide optimal blood pressure control.[39] Another option is metyrosine (tyrosine hydroxylase inhibitor), which blocks the rate-limiting step of catecholamine synthesis. The above medications are generally started 10 to 14 days prior to surgery, with a goal blood pressure of less than 160/90 mm Hg.

SURGICAL MANAGEMENT

In 1926, Cesar Roux in Switzerland and Charles H. Mayo in the United States were credited with curing pheochromocytoma by surgical resection.[23] Currently, unilateral pheochromocytoma is routinely treated with unilateral adrenalectomy (laparoscopic or open based on size). With technologic advances and greater experience with laparoscopic surgery, there is now less intraoperative hypotension, less hypotensive episodes, and a faster postoperative course compared with the open approach.[40] Bilateral and/or metastatic pheochromocytoma are challenging therapeutic dilemmas. Debulking surgery and systemic chemotherapy or ^{123}I MIBG therapy often require the involvement of multiple subspecialty physicians at specialty care hospitals. A detailed discussion of theses modalities is beyond the scope of this article.

POSTOPERATIVE CARE AND FOLLOW-UP

Surprisingly, even after successful surgery, 27% to 38% of patients continue to have residual nonparoxysmal hypertension,[10] necessitating continual surveillance and treatment of any persistent hypertension. In 10% to 15% of patients, transient hypoglycemia can occur due to the removal of catecholamine suppression of insulin secretion.[23] These patients require frequent

glucose monitoring and can be treated with 5% dextrose intravenous solution if necessary. Plasma metanephrine levels should be measured at 6 weeks and again at 6 months after surgery in all patients.[10] Although the risk is low, tumor recurrence can also occur with sporadic pheochromocytomas. Therefore, annual biochemical tests and a physical examination should be continued for a minimum of 5 years in these patients.[4] Meticulous follow-up must be implemented for hereditary forms of pheochromocytoma because of the increased risk of tumor recurrence. The 5-year patient survival after tumor removal for benign pheochromocytoma is between 84% to 96%.[4]

CONCLUSION

Despite its low incidence, the diagnosis of pheochromocytoma must be considered in numerous clinical situations because it causes such a wide range of symptoms. Furthermore, if these tumors are not quickly recognized, life-threatening complications can occur. Genetic screening for mutations of RET, VHL, SDHD, and SDHB is an important step in the early diagnosis and prevention of severe cardiovascular disease. Genetic testing should be offered to first-degree relatives of patients with germline mutations in RET, VHL, NF1, SDHD, and SDHB; patients with bilateral or multifocal tumors; patients with malignant or extra-adrenal pheochromocytoma; and patients who are aged 50 years or younger when diagnosed. Current guidelines do not recommend the use of multiple biochemical tests to exclude pheochromocytoma; instead, it is best to order a single test of plasma free metanephrine. If the plasma metanephrine test is unavailable, urinary fractionated metanephrine is a suitable alternative. As CT and MRI are readily available, they should be used as first-line imaging modalities for localizing pheochromocytoma.

Phenoxybenzamine, followed by β-blockade, is commonly used for preoperative preparation. However, calcium channel blockers and α_1-blockers can be used instead of phenoxybenzamine to avoid the adverse effects of nonspecific α-blockers. Surgical resection is the treatment of choice for most pheochromocytomas. Postoperative follow-up should include annual biochemical tests and a physical examination for at least 5 years. More frequent monitoring is required for patients with hereditary forms of pheochromocytoma. **HP**

Test your knowledge and comprehension of this article with the *Clinical Review Quiz* on page 55.

REFERENCES

1. Manger WM. Editorial: In search of pheochromocytomas [editorial]. J Clin Endocrinol Metab 2003;88: 4080–2.
2. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev 2004;25:458–511.
3. Dluhy RG. Pheochromocytoma—death of an axiom [editorial]. N Engl J Med 2002;346:1486–8.
4. Walther MM, Keiser HR, Linehan WM. Pheochromocytoma: evaluation, diagnosis, and treatment. World J Urol 1999;17:35–9.
5. Hernandez FC, Sanchez M, Alvarez A, et al. A five-year report on experience in the detection of pheochromocytoma. Clin Biochem 2000;33:649–55.
6. Elder EE, Elder G, Larsson C. Pheochromocytoma and functional paraganglioma syndrome: no longer the 10% tumor. J Surg Oncol 2005;89:193–201.
7. Neumann HP, Bausch B, McWhinney SR, et al. Germline mutations in nonsyndromic pheochromocytoma. Freiburg-Warsaw-Columbus Pheochromocytoma Study Group. N Engl J Med 2002;346:1459–66.
8. Kim WY, Kaelin WG. Role of VHL gene mutation in human cancer. J Clin Oncol 2004;22:4991–5000.
9. Dannenberg H, van Nederveen FH, Abbou M, et al. Clinical characteristics of pheochromocytoma patients with germline mutations in SDHD. J Clin Oncol 2005;23: 1894–901.
10. Pacak K, Linehan WM, Eisenhofer G, et al. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med 2001;134:315–29.
11. Walther MM, Reiter R, Keiser HR, et al. Clinical and genetic characterization of pheochromocytoma in von Hippel-Lindau families: comparison with sporadic pheochromocytoma gives insight into natural history of pheochromocytoma. J Urol 1999;162(3 Pt 1):659–64.
12. Witteles RM, Kaplan EL, Roizen MF. Sensitivity of diagnostic and localization tests for pheochromocytoma in clinical practice. Arch Intern Med 2000;160:2521–4.
13. Gifford RW Jr, Manger WM, Bravo EL. Pheochromocytoma. Endocrinol Metab Clin North Am 1994;23: 387–404.
14. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. Endocr Rev 2003;24:539–53.
15. Raber W, Raffesberg W, Bischof M, et al. Diagnostic efficacy of unconjugated plasma metanephrines for the detection of pheochromocytoma. Arch Intern Med 2000;160: 2957–63.
16. Sawka AM, Jaeschke R, Singh RJ, Young WF Jr. A comparison of biochemical tests for pheochromocytoma: measurement of fractionated plasma metanephrines compared with the combination of 24-hour urinary metanephrines and catecholamines. J Clin Endocrinol Metab 2003;88: 553–8.
17. Crout JR, Sjoerdsma A. Turnover and metabolism of

catecholamines in patients with pheochromocytoma. J Clin Invest 1964;43:94–102.
18. Sweeney AT, Malabanan AO, Blake MA, et al. Megacolon as the presenting feature in pheochromocytoma. J Clin Endocrinol Metab 2000;85:3968–72.
19. Mann SJ. Severe paroxysmal hypertension (pseudopheochromocytoma): understanding the cause and treatment. Arch Intern Med 1999;159:670–4.
20. Eisenhofer G, Goldstein DS, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. J Clin Endocrinol Metab 2003;88:2656–66.
21. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. J Clin Endocrinol Metab 2004;89:479–91.
22. Lenders JW, Pacak K, Walther MM, et al. Biochemical diagnosis of pheochromocytoma: which test is best? JAMA 2002;287:1427–34.
23. Kudva YC, Sawka AM, Young WF Jr. Clinical review 164: The laboratory diagnosis of adrenal pheochromocytoma: the Mayo Clinic experience. J Clin Endocrinol Metab 2003;88:4533–9.
24. Caoili EM, Korobkin M, Francis IR, et al. Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 2002;222:629–33.
25. Korobkin M, Brodeur FJ, Francis IR, et al. CT time-attenuation washout curves of adrenal adenomas and nonadenomas. AJR Am J Roentgenol 1998;170:747–52.
26. Blake MA, Krishnamoorthy SK, Boland GW, et al. Low-density pheochromocytoma on CT: a mimicker of adrenal adenoma. AJR Am J Roentgenol 2003;181:1663–8.
27. Ilias I, Yu J, Carrasquillo JA, et al. Superiority of 6-[18F]-fluorodopamine positron emission tomography versus [131I]-metaiodobenzylguanidine scintigraphy in the localization of metastatic pheochromocytoma. J Clin Endocrinol Metab 2003;88:4083–7.
28. Mannelli M, Ianni L, Cilotti A, Conti A. Pheochromocytoma in Italy: a multicentric retrospective study. Eur J Endocrinol 1999;141:619–24.
29. Fink IJ, Reinig JW, Dwyer AJ, et al. MR imaging of pheochromocytomas. J Comput Assist Tomogr 1985;9:454–8.
30. Shulkin BL, Thompson NW, Shapiro B, et al. Pheochromocytomas: imaging with 2-[fluorine-18]fluoro-2-deoxy-D-glucose PET. Radiology 1999;212:35–41.
31. van der Harst E, de Herder WW, Bruining HA, et al. [123I]metaiodobenzylguanidine and [(111)In] octreotide uptake in benign and malignant pheochromocytomas. J Clin Endocrinol Metab 2001;86:685–93.
32. Lynn MD, Shapiro B, Sisson JC, et al. Pheochromocytoma and the normal adrenal medulla: improved visualization with I-123 MIBG scintigraphy. Radiology 1985; 155:789–92.
33. Tsuchimochi S, Nakajo M, Nakabeppu Y, Tani A. Metastatic pulmonary pheochromocytomas: positive I-123 MIBG SPECT with negative I-131 MIBG and equivocal I-123 MIBG planar imaging. Clin Nucl Med 1997;22: 687–90.
34. Shulkin BL, Shapiro B, Francis IR, et al. Primary extra-adrenal pheochromocytoma: positive I-123 MIBG imaging with negative I-131 MIBG imaging. Clin Nucl Med 1986;11:851–4.
35. Pacak K, Goldstein DS, Doppman JL, et al. A "pheo" lurks: novel approaches for locating occult pheochromocytoma. J Clin Endocrinol Metab 2001;86:3641–6.
36. Eisenhofer G, Bornstein SR, Brouwers FM, et al. Malignant pheochromocytoma: current status and initiatives for future progress. Endocr Relat Cancer 2004;11:423–36.
37. Bravo EL. Pheochromocytoma: an approach to antihypertensive management. Ann N Y Acad Sci 2002;970:1–10.
38. Boutros AR, Bravo EL, Zanettin G, Straffon RA. Perioperative management of 63 patients with pheochromocytoma. Cleve Clin J Med 1990;57:613–7.
39. Proye C, Thevenin D, Cecat P, et al. Exclusive use of calcium channel blockers in preoperative and intraoperative control of pheochromocytomas: hemodynamics and free catecholamine assays in ten consecutive patients. Surgery 1989;106:1149–54.
40. Sprung J, O'Hara JF Jr, Gill IS, et al. Anesthetic aspects of laparoscopic and open adrenalectomy for pheochromocytoma. Urology 2000;55:339–43.