Pheochromocytomas are rare, catecholamine-secreting tumors that represent a potentially curable form of endocrine hypertension. The estimated incidence ranges from 0.005% to 0.1% of the general population and from 0.1% to 0.2% of the adult hypertensive population [1]. This incidence accounts for approximately three to four cases per million population in the United States diagnosed yearly. Greater than 90% of pheochromocytomas arise intra-abdominally, most frequently in the chromaffin cells of the adrenal medulla. Approximately 10% are found in extra-adrenal sites where they are more appropriately called paragangliomas because of their association with ganglia of the sympathetic nervous system. The organ of Zuckerkandl located between the aortic bifurcation and the inferior mesenteric artery is a common extra-adrenal site. This review discusses recent advances regarding the genetics of pheochromocytoma, the biochemical diagnosis, localization by imaging studies, and surgical management. The authors also address the management of malignant pheochromocytoma.

**GENETICS**

Approximately 10% of pheochromocytomas are hereditary. Hereditary tumors differ from sporadic tumors in that they are frequently multiple or bilateral and rarely malignant [2]. Familial syndromes associated with pheochromocytomas include multiple endocrine neoplasia type 2 (MEN 2), von Hippel-Lindau disease (VHL), and the neuroectodermal dysplasias consisting of neurofibromatosis, tuberous sclerosis, and Sturge-Weber syndrome. Recently, mutations in the succinate dehydrogenase (SDH) genes have also been identified as resulting in a familial paraganglioma syndrome.

MEN 2 is the best studied of these familial syndromes. Pheochromocytoma in MEN 2 is associated with germline mutations in the *RET* gene.

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proto-oncogene, most often involving codons 634 and 918 [3–6]. This activating mutation in the \textit{RET} gene drives abnormal cellular proliferation that leads to adrenal medullary hyperplasia and pheochromocytoma [7]. Pheochromocytomas develop in approximately 50% of patients with MEN 2 [8,9]. They are rarely extra-adrenal, are most often benign, and are usually diagnosed before the age of 40 years. Approximately one quarter to one third of patients have bilateral pheochromocytomas at the time of diagnosis [6,10]. Even if it is not clinically apparent on presentation, most MEN 2 patients have bilateral disease at the cellular level [11]; therefore, it is not surprising that approximately 50% of MEN 2 patients who undergo surgical resection of a unilateral pheochromocytoma develop clinical evidence of bilateral disease within 10 years [9,12]. Occasionally, pheochromocytoma is the first manifestation of the MEN syndrome. More often, these patients are identified after the diagnosis of medullary thyroid cancer (MTC), which has higher penetrance [2,3]. At the University of Texas M. D. Anderson Cancer Center, the authors have recently reported their experience with 39 patients diagnosed with pheochromocytoma in association with MEN 2A. The median age at diagnosis was 36 years with a range of 19 to 60 years. In nine (23%) patients, pheochromocytoma was diagnosed concomitantly with MTC, whereas in six (15%) patients, pheochromocytoma was the initial manifestation of the syndrome [13]. In 18 (46%) patients, the diagnosis was made when the patient was still asymptomatic. This observation is attributable to the diagnosis being dependent on the age at which routine screening is initiated rather than the age at which symptoms develop [13]. The authors recommend yearly evaluation with plasma metanephrines for all patients with MEN 2.

\textit{VHL} disease is a second familial syndrome associated with pheochromocytoma. The \textit{VHL} gene is a tumor suppressor gene, and germline mutations result in the development of the syndrome [14]. Affected persons develop early onset bilateral kidney tumors and cysts, pheochromocytomas, cerebellar and spinal hemangioblastomas, retinal angiomas, pancreatic cysts and tumors, epididymal cystadenomas, and tumors in the endolymphatic sac canal of the inner ear [15]. Approximately 56% of \textit{VHL} families have pheochromocytoma, and they are classified as type 2A or 2B depending on the absence or presence of renal carcinoma. \textit{VHL} families without pheochromocytoma are classified as \textit{VHL} type 1 [16]. With respect to the development of pheochromocytoma, missense mutations in the \textit{VHL} gene are associated with the development of these tumors more than twice as often as other types of mutations [17,18]. In a recent review of the authors’ experience, 40 patients with \textit{VHL} were identified from 24 pedigrees. Ten (25%) patients had pheochromocytomas, the majority (70%) of which were diagnosed at age 40 years or younger. Four (40%) patients had bilateral disease. There were no cases of malignant disease. Of patients in whom the results of genetic testing were available, 50% with a missense mutation had a pheochromocytoma. Conversely, no patient with non-missense mutations developed a pheochromocytoma [19].
A small number of families with familial pheochromocytomas have neither RET or VHL germline mutations. Recently, it was discovered that patients with germline mutations in three of the SDH (mitochondrial complex II) subunits (SDHD, SDHB, and SDHC) have increased susceptibility to head and neck paragangliomas typified by carotid body glomus tumors [20]. SDH-defined disease was subsequently expanded to include pheochromocytomas which were found to occur in patients with SDHB and SDHD mutations [21,22].

Recent studies suggest that almost one quarter of patients with apparently sporadic pheochromocytoma are actually mutation carriers. In a study of 271 patients who presented with nonsyndromic pheochromocytoma and without a family history of the disease, Neumann and colleagues [23] found mutations in 66 (25%). Thirty patients had mutations of the VHL gene, 13 of the RET gene, 11 of SDHD, and 12 of SDHB. A younger age and multifocal tumors were significantly associated with the presence of a mutation. Of the 13 patients testing positive for the RET proto-oncogene, none had clinical evidence of MTC at presentation, but in 12 patients (92%), the disease developed during the follow-up period. Among the 30 carriers of VHL mutations, 10 (33%) were subsequently diagnosed with other features associated with VHL disease. Similarly, of the 23 carriers of SDHD or SDHB mutation, none had glomus tumors at presentation, but these tumors developed in four patients (17%) during the follow-up period [23]. Because almost one quarter of patients with apparently sporadic pheochromocytomas actually harbor mutations, Neumann and colleagues advocate routinely analyzing for mutations to identify pheochromocytoma-associated syndromes that would otherwise be missed [23].

In a second study investigating apparently sporadic pheochromocytomas, Gimenez-Roqueplo and colleagues [24] found that 12% of patients had a genetic mutation, 2% in the VHL gene and 10% in the SDHB gene. The authors recommend screening patients less than 25 years old who present with a pheochromocytoma in the absence of any obvious family history. In the absence of additional information, we begin by screening for VHL and SDHB genes. If a disease-associated mutation is found, we advocate lifelong surveillance, prophylactic surgery (ie, total thyroidectomy with central lymph node dissection in patients with MEN 2 as identified by a RET mutation), or both, depending on the precise genetic diagnosis. For instance, in patients with MEN 2, prophylactic thyroidectomy should be performed. In addition, all first-degree relatives of the identified carrier should undergo genetic testing to determine the presence or absence of a family-specific mutation.

**CLINICAL PRESENTATION AND DIAGNOSIS**

Periodic screening in patients with hereditary pheochromocytoma may lead to early diagnosis when tumors are small and asymptomatic. It is uncommon for patients with sporadic pheochromocytoma not to demonstrate some characteristic sign or symptom of the disease. The most common clinical presentation is
hypertension that is new onset, refractory, paroxysmal, or recently exacerbated. This symptom in combination with headaches, excessive sweating, pallor, flushing, or palpitations should prompt an evaluation for pheochromocytoma. Less common symptoms include nausea, lassitude, heat intolerance, anxiety, nervousness, abdominal pain, fever, or the glucose intolerance of diabetes [25,26]. Another finding that should prompt an evaluation for pheochromocytoma is the identification of an incidental adrenal mass identified on radiographic studies obtained for nonendocrine clinical disorders. Such adrenal incidentalomas are found in 1% to 4% of patients undergoing abdominal imaging studies [27].

Making the diagnosis of pheochromocytoma depends on demonstrating excessive production of catecholamines. In general, there is a low pretest prevalence of pheochromocytoma of approximately 0.5% in persons tested owing to hypertension and suggestive symptoms [28] and 4% in persons with a radiographically identified adrenal incidentaloma [29]. This low prevalence combined with the imperfect sensitivity and specificity of commonly used biochemical tests can make the diagnosis of pheochromocytoma difficult. Making the diagnosis is critical, because undiagnosed and untreated pheochromocytoma can have devastating consequences due to the potentially excessive release of catecholamines. In a series of patients with pheochromocytoma discovered at autopsy, 75% died suddenly from myocardial infarction or cerebrovascular catastrophe. Approximately one third of these sudden deaths occurred during or immediately after unrelated minor operations [30]; therefore, the chosen biochemical test must be reliable in excluding pheochromocytoma. A false-positive result can be refuted by additional tests, whereas a false-negative result subjects the patient to the risks associated with an undiagnosed and untreated pheochromocytoma which can be fatal [31].

Traditionally, 24-hour urinary measurement for catecholamines, total and fractionated metanephrines, and vanillylmandelic acid (VMA) has been used to screen patients for pheochromocytoma. More recent studies suggest that measurement of plasma free metanephrines is a superior test for confirming or excluding the diagnosis [32–34]. This test is based on the fact that, while pheochromocytomas secrete catecholamines only episodically, these tumors metabolize catecholamines continuously; therefore, metanephrine concentrations should be consistently high in the serum in the presence of a tumor, even if catecholamine release is paroxysmal [35,36].

Lenders and colleagues [33] recently reported the results of a multicenter cohort study of patients tested for pheochromocytoma at four referral centers from 1994 to 2001. They compared commonly used tests such as measurement of plasma and urinary catecholamines, urinary fractionated metanephrines, urinary total metanephrines, and urinary VMA with measurements of plasma free metanephrines. Table 1 summarizes the sensitivity and specificity for the indicated test. Measurements of urinary fractionated metanephrines and plasma free metanephrines have comparable high sensitivity; therefore, a negative result for either test would effectively exclude a pheochromocytoma. Because of
superior specificity, plasma free metanephrines exclude pheochromocytoma in many more patients without the disease than does measurement of urinary fractionated metanephrines [33]. The false-negative plasma free metanephrine rate was 1.4% [33]. Lenders and colleagues recommend plasma metanephrines as the initial biochemical test in all patients being evaluated for pheochromocytoma.

Other authorities advocate a different approach determined by the pretest probability that the patient has a pheochromocytoma. Sawka and colleagues investigated the diagnostic efficacy of different tests comparing fractionated plasma metanephrine measurements with measurements of 24-hour urinary total metanephrines and catecholamines. They identified a higher sensitivity for plasma metanephrines of 97% versus 90% for urinary total metanephrines and catecholamines. Specificity was better for urinary measurements, with a rate of 98% versus 85% for plasma metanephrines. They recommend measurement of 24-hour urinary total metanephrines and catecholamines as the preferred diagnostic modality in low-risk patients. This test will result in fewer false-positive results that prompt further unnecessary evaluation. In higher risk patients such as those with a familial predisposition, they recommend measurement of plasma metanephrines [37].

Other studies have confirmed the utility of an approach that measures plasma metanephrine and normetanephrine in patients with a genetic predisposition to developing pheochromocytoma. In the previously mentioned study by Lenders and colleagues [33], the sensitivity and specificity for hereditary tumors were 97% and 96%, respectively. For sporadic tumors, the sensitivity and specificity were 99% and 82%. In a study of patients with VHL or MEN 2, Eisenhofer and colleagues [32] compared plasma concentrations of normetanephrine and metanephrine with urinary measurements of catecholamines, metanephrines, and VMA. The sensitivity of measurements of plasma normetanephrine and metanephrine for the detection of tumors was 97%, whereas the other biochemical tests had a sensitivity of 47% to 74%.

At the University of Texas M. D. Anderson Cancer Center, the authors prefer to evaluate patients with plasma metanephrines. In addition to having

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superior sensitivity, this test is less cumbersome for the patient than studies of urinary catecholamines and metabolites which requires a 24-hour urine collection. Before testing, patients are asked to fast and abstain from caffeinated beverages. Acetaminophen should not be taken for 5 days before the test because it can interfere with the plasma normetanephrine assay [38]. On the day of testing, patients rest supine for 20 minutes after which their blood is drawn. Levels of plasma metanephrines greater than 96 pg/mL, plasma normetanephrine greater than 130 pg/mL, or total metanephrines greater than 200 are considered abnormal.

**TUMOR LOCALIZATION**

Appropriate treatment of pheochromocytoma depends on tumor localization after biochemical confirmation of the diagnosis. Conventional imaging modalities that have been used in the preoperative evaluation of patients with a biochemically confirmed pheochromocytoma include CT, MRI, and 131I-metaiodobenzylguanidine (131I-MIBG) scintigraphy. CT has the advantages of moderate cost and high sensitivity, which varies between 93% and 100% for detecting tumors in the adrenal gland and approximately 90% for identifying extra-adrenal disease [38–44]. In the authors’ experience, high-quality spiral CT scans can depict up to 95% of adrenal masses; therefore, a dedicated adrenal protocol CT scan through the abdomen and pelvis is the initial imaging study [1]. The adrenal protocol includes unenhanced CT followed by contrast-enhanced and delayed contrast-enhanced images obtained with 2- to 5-mm thick scanning sections. Lesions 0.5 cm or larger can routinely be detected. Fig. 1 depicts a 1.5-cm right sided pheochromocytoma on contrast-enhanced images.

MRI is another widely used imaging modality. It has the advantage of not exposing the patient to ionizing radiation and elimination of contrast media as well as having sensitivity comparable with that of CT in detecting adrenal disease. The sensitivity for identifying extra-adrenal disease is approximately 90% [38,39,45]. Characterization of adrenal masses is done with chemical shift

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**Fig. 1.** CT scan with contrast enhancement showing a 1.5-cm right adrenal mass (arrow).
MRI based on the presence of fat in benign adenomas and the absence of fat in pheochromocytomas [40]. In addition, the hypervascularity of pheochromocytomas makes them appear characteristically bright, with a high signal on T2-weighted images and no signal loss on opposed-phase images (Fig. 2) [46]. The authors perform MRI in patients with a biochemically proven pheochromocytoma and a negative CT. MRI can also be a valuable adjunct in evaluating patients with a pheochromocytoma near the great vessels. Because of the ability to obtain multiplanar imaging, MRI is superior to CT in the assessment of the relationship between the tumor and the surrounding vessels; therefore, it may be helpful in identifying vascular invasion [42].

Both CT and MRI have poor specificity, as low as 50% in some reports [42]. In contrast, $^{131}$I-MIBG scanning offers specificity ranging from 95% to 100%, but it has lower sensitivity [41–43,47,48]. $^{131}$I-MIBG scanning works by administering a radiolabeled amine for which chromaffin tissue is selectively avid. Because it is a physiologic study, MIBG can identify pheochromocytomas regardless of their location. This modality may be useful in patients with biochemical evidence of a pheochromocytoma that has not been localized by CT or MRI or in the follow-up evaluation of patients with suspected or documented recurrent or metastatic disease. One significant drawback of $^{131}$I-MIBG scanning is the complexity of the examination. To prevent thyroid ablation, the gland must be blocked by giving a saturated solution of potassium iodide or potassium perchlorate before and after administration of the radioactive iodine. Also, repeat scans may be required for up to 72 hours to obtain optimal images. Because it is a physiologic and not anatomic study, findings require correlation with CT or MRI. The potential for fusion imaging combining MIBG scanning with CT or MRI has been investigated and has diagnostic potential in the evaluation of patients with pheochromocytoma [49]. The authors reserve $^{131}$I-MIBG scanning for use in patients with biochemical evidence of pheochromocytoma in whom CT or MRI has failed to identify the tumor. It may also be helpful in patients with distorted anatomy owing to previous

Fig. 2. T2-weighted MR image showing left adrenal mass (arrow). The hypervascularity of pheochromocytomas makes them appear characteristically bright.
surgery or with equivocal biochemical diagnoses. Other authorities have advocated using \(^{131}\text{I-MIBG}\) scanning selectively in patients with tumors larger than 5 cm, or if there is suspicion for metastatic tumor [50]. MIBG scanning can also be performed using the iodine isotope \(^{123}\text{I}\). The primary advantage of \(^{123}\text{I-MIBG}\) is that images are obtained using single-photon emission CT (SPECT), which offers improved sensitivity over planar imaging [51]. Currently, the availability of \(^{123}\text{I-MIBG}\) in the United States is limited.

Positron emission tomography (PET) studies have also been investigated for the imaging of pheochromocytoma. PET with \([^{18}\text{F-FDG}]\) has been successful, particularly in imaging metastatic disease; however, because all rapidly metabolizing tumor cells take up glucose, it is nonspecific [50,52]. Scanning with more specific ligands such as \([^{11}\text{C-hydroxyephedrine}]\) and \([^{11}\text{C-adrenaline}]\) detect pheochromocytomas; however, their short half-life and high cost for on-site production make it unlikely that they will have widespread application [53,54]. Other investigators have shown that radiolabeled dopamine is an excellent agent to localize pheochromocytomas [40]. Low radiation exposure and superior spatial resolution are important advantages of PET; however, its cost and limited availability are significant drawbacks that limit the widespread application of this imaging modality [40].

**TREATMENT**

Surgical resection is the definitive treatment for patients with pheochromocytoma. Before proceeding with surgery, the patient must be adequately prepared with alpha-adrenergic blockade and complete restoration of fluid and electrolyte balance. Alpha blockade works to oppose catecholamine-induced vasoconstriction. Traditionally, phenoxybenzamine, a long-acting nonselective noncompetitive blocker, has been most commonly used. A dose of 10 mg orally taken twice daily is initiated at the time of diagnosis. This dose can be increased gradually over a 1- to 3-week period until adequate blockade, as evidenced by the development of orthostatic hypotension, is obtained. The total dose should not exceed 2 mg/kg/day. Selective alpha\(_1\)-adrenergic blockers such as prazosin and terazosin have also been used. One potential advantage of selective alpha\(_1\) blockade is the preservation of the alpha\(_2\) catecholamine reuptake mechanism [55].

Patients with pheochromocytoma also experience volume contraction from chronic vasoconstriction; therefore, liberal salt and fluid intake are encouraged to promote intravascular expansion. This volume expansion preoperatively helps to minimize intraoperative blood pressure lability. Ten days to 2 weeks of this preoperative preparation before surgery is recommended. With appropriate alpha blockade and restoration of intravascular volume, some patients experience reflex tachycardia which can be treated with beta blockade. Beta blockade should not be instituted unless alpha blockade is established owing to the risk that beta blockade will inhibit epinephrine-induced vasodilation, leading to more significant hypertension, left-sided heart strain, congestive heart failure, and pulmonary edema. Without appropriate preoperative
preparation, the induction of anesthesia, tumor manipulation, or other stimulation can result in massive intraoperative outpouring of catecholamines with subsequent hypertensive crisis and possible stroke, arrhythmia, or myocardial infarction. Before the introduction of preoperative alpha blockade, such complications were common, and surgical mortality rates ranged from 24% to 50% [56,57]. In refractory cases, metyrosine, a tyrosine hydroxylase inhibitor, can be added to manage hypertensive crises. Doses are up to 750 mg every six hours.

Even with appropriate preoperative preparation, catecholamine release with resultant hypertensive crisis or tachyarrhythmia may occur with surgical manipulation of the tumor-containing adrenal gland. Ligation of the adrenal vein during surgical extirpation can cause abrupt cessation of catecholamine release which can lead to acute hypotension. Patients should have adequate peripheral and central venous access established as well as a radial artery catheter and, in selected patients, a pulmonary artery catheter. Intravenous titratable pharmacologic agents should be mixed and ready for infusion. Sodium nitroprusside is the agent of choice for rapid control of acute hypertension. It is a direct-acting vasodilator that can be titrated to provide nearly second-by-second blood pressure control. Epinephrine and norepinephrine are the agents of choice to treat hypotension after adrenal vein ligation. Good communication between the operating surgeon and the anesthesiologist is critical during the procedure.

The surgical procedure performed depends on whether the tumor is sporadic or hereditary and whether it is unilateral or bilateral. In patients with sporadic pheochromocytoma, approximately 90% of the tumors are unilateral, and the authors’ treatment of choice for tumors less than 6 cm in size is a laparoscopic adrenalectomy. The laparoscopic approach has been shown to be safe with similar blood loss and no difference in blood pressure and heart rate increments when compared with open adrenalectomy [58]. Patients also experience faster resolution of postoperative ileus, decreased analgesic requirements, a shorter length of hospital stay, and a shorter convalescence with a quicker return to normal activity [59–63]. With respect to laparoscopic resection of pheochromocytoma, most reports describe a transperitoneal approach. A recent report by Walz and colleagues [64] describes a posterior retroperitoneal approach that allows direct access to the adrenal glands. They have used this approach in 127 operations for pheochromocytoma and have found that it is not only feasible and safe but also faster and less painful. For tumors greater than 6 cm in size, the authors perform open adrenalectomy because of the increased risk of malignancy, which is reported to be up to 25% [1].

Patients with familial pheochromocytoma present a greater challenge in that they often have bilateral disease at the time of presentation, or if they have a unilateral tumor at presentation, they are at risk for the development of contralateral disease in the future. Historically, some authorities have advocated bilateral total adrenalectomy as appropriate therapy for patients with familial pheochromocytoma because that procedure would prevent the development of recurrent disease and eliminate the risk of catecholamine crisis and distant
metastases \[65,66\]. Unfortunately, after bilateral total adrenalectomy, the patient is committed to lifelong steroid hormone replacement therapy and the subsequent risk of acute adrenal insufficiency, which occurs in 25% to 33% of patients \[12,67\].

For patients with inherited pheochromocytoma, the authors consider cortical-sparing adrenalectomy. This strategy is based on three important points. First, the remaining cortex left in situ may prevent the need for chronic corticosteroid replacement, minimizing the risk of adrenal insufficiency. In a recent series from our institution, cortical-sparing adrenalectomy prevented the need for chronic corticosteroid replacement in the majority (65%) of patients, and only one patient experienced acute adrenal insufficiency \[13\]. Second, metastatic pheochromocytoma rarely occurs in patients with inherited pheochromocytoma syndromes. Of 56 patients with familial pheochromocytoma treated at the M. D. Anderson Cancer Center, none have developed malignant disease \[13\]. In addition, the risk of a malignant pheochromocytoma in MEN 2 or VHL is usually kindred specific, making malignancy unlikely in the absence of a positive family history \[68,69\]. Third, the risk of recurrent pheochromocytoma in the remnant adrenal gland treated with a cortical-sparing technique is acceptably low. In the authors’ series, recurrent disease developed in an adrenal remnant in 10% of patients who underwent unilateral or bilateral cortical-sparing surgery. The median time to recurrence was 4.6 years (1.8–20.3 years) from the time of initial surgery \[13,70\].

From a technical standpoint, a successful cortical-sparing procedure requires several key elements. Accurate preoperative imaging is required to identify the portion of the cortex most likely to be spared. The arterial supply to the adrenal gland includes small tributaries from the aorta, renal artery, and inferior phrenic artery. In the authors’ experience, the cephalad aspect of the adrenal gland based on the phrenic circulation is most suitable for subtotal adrenal preservation in situ. At the time of surgery, exposure of the adrenal gland in a bloodless field is important. Using the more standard transperitoneal approach, to gain access to the right adrenal, the liver must be mobilized to expose the intra-abdominal inferior vena cava and allow for full visualization of the gland. On the left, the spleen and distal pancreas must be mobilized such that the left renal vein at its junction with the adrenal vein is easily visualized. It is critically important that the portion of the adrenal gland to be preserved in situ be mobilized out of the retroperitoneum, especially when ligation of the adrenal vein is required as is true in the majority of patients \[13\]. For this reason, the authors currently prefer to perform cortical-sparing adrenalectomy as an open procedure which allows transection of the adrenal gland without full mobilization \[13,71\]. Others have reported performing cortical-sparing adrenalectomy laparoscopically by both a transperitoneal \[72,73\] and a retroperitoneal approach \[74\]. Our concern with respect to the transperitoneal laparoscopic approach is that it involves more extensive mobilization of the adrenal gland which may result in devascularization of the adrenal cortex to be preserved in situ. The retroperitoneal approach allows more direct
visualization of the adrenal gland, allowing clear differentiation between normal and neoplastic adrenal tissue. It also allows one to identify and secure the adrenal vein without extensive mobilization, thereby decreasing the subsequent risk of devascularization of the cortex to be preserved; therefore, the posterior retroperitoneal laparoscopic approach may be appropriate for performing cortical-sparing adrenalectomy.

For patients with familial pheochromocytoma, we have implemented the following surgical strategy. For patients with a unilateral tumor and a normal contralateral gland, a laparoscopic total adrenalectomy is performed. For patients who present with bilateral disease, a midline incision is used to perform a unilateral cortical-sparing procedure with removal of the entire contralateral gland. The risk of recurrent disease is less by preserving cortex on only one side in comparison with preserving cortex bilaterally. Fig. 3 depicts the preoperative CT scan (Fig. 3A) and ex vivo intraoperative photographs (Fig. 3B) from a patient with MEN 2 who presented with bilateral tumors and underwent a cortical-sparing procedure on the left with resection of the entire right adrenal gland. For patients who present with a metachronous contralateral pheochromocytoma after a previous unilateral adrenalectomy, we perform an open cortical-sparing procedure. Long-term follow-up includes yearly plasma or urinary screening studies to monitor the remaining adrenal gland or portion of adrenal gland for recurrent disease [13].

MALIGNANT PHEOCHROMOCYTOMA

To make the diagnosis of malignant pheochromocytoma, one must document invasion of adjacent organs or metastatic disease. The most frequent sites of metastases are the liver, lung, and bone, particularly the spine, skull, and ribs. Approximately 15% of pheochromocytomas exhibit malignant behavior, with 10% of patients having metastatic disease at the time of presentation [39,75]. Others with apparently benign, sporadic, well-encapsulated tumors have acquired distant metastases over time that have proven fatal [76].

Fig. 3. (A) Preoperative CT scan obtained in a patient with MEN 2 presenting with bilateral pheochromocytomas. (B) Ex vivo operative photographs.
There are no absolute clinical, imaging, or laboratory criteria to predict malignancy [39,40,47,75,77]; however, patients with malignant disease tend to have larger tumors, higher urinary metanephrine levels, and a shorter duration of presenting symptoms [78]. The 10-year survival rate for patients with malignant pheochromocytoma is approximately 40% [79].

Surgical resection is the treatment of choice for patients with malignant pheochromocytoma. If the disease is limited at the time of diagnosis, surgical resection can be undertaken with curative intent [79]. If disease is more extensive, surgery is undertaken for tumor debulking and palliation [80]. In the later situation, it is likely that tumors will recur locally. Surgical treatment for these locally recurrent tumors is again recommended for palliation [78].

For patients with unresectable disease, the initial therapeutic option is 131I-MIBG. This therapy is generally more effective in the treatment of soft tissue metastases than bone metastases. Treatment consists of single doses ranging from 3.7 to 9.1 GBq administered intravenously over 2 to 3 hours with cumulative doses reaching up to 85.9 GBq. Patients are treated for 3 to 6 months, with re-evaluation with biochemical analysis and MIBG imaging performed before each treatment course. The treatment is well tolerated with minimal toxicity. Hormonal responses are seen in as many as 45% of patients and tumor responses in 30% [79,81]. 131I-MIBG treatment is effective palliation and improves quality of life. In patients who experience tumor arrest or regression, such therapy can also prolong survival [82].

Unfortunately, not all patients with malignant pheochromocytomas have sufficient uptake of MIBG to allow MIBG therapy. In these patients, cytotoxic chemotherapy may have some therapeutic benefit. The most commonly used chemotherapeutic regimen uses cyclophosphamide, vincristine, and dacarbazine. In their initial study describing the treatment of 14 patients, Averbuch and colleagues [83] reported a complete tumor response in two patients and a partial response in six. One patient experienced progression of disease. Overall, treatment with chemotherapeutic regimens has been disappointing with response rates of less than 50% [84]. Recently, combination treatment strategies with MIBG and chemotherapy have been studied. There are two reasons to explore such combination therapy. First, in many patients, MIBG-positive lesions coexist with MIBG-negative lesions [85]. Second, data from in vitro experiments suggest that treatment with cytotoxic chemotherapeutic agents may increase uptake of MIBG in neuroendocrine tumor cells [86]. In a recent series of six patients treated at the University of Michigan with combination 131I-MIBG and chemotherapy, Sisson and colleagues [87] showed evidence for the additive effects of the two therapies.

New therapeutic strategies are being investigated. For instance, vascular endothelial growth factor (VEGF) expression has been found to be significantly higher in metastatic pheochromocytomas when compared with benign tumors. This finding suggests that VEGF-mediated angiogenesis may be related to tumor progression. In malignant pheochromocytoma cell cultures, neutralizing anti-VEGF monoclonal antibodies have been shown to inhibit angiogenesis,
suggesting a possible role in the treatment of nonresectable pheochromocytomas [88].

**SUMMARY**

Pheochromocytomas continue to be rare tumors. Whereas historical data suggest that approximately 10% of pheochromocytomas are hereditary, more recent studies suggest that up to one quarter of tumors thought to be sporadic actually occur in mutation carriers. This finding has significant implications for the diagnosis and management of these patients.

The authors advocate using plasma metanephrine levels (sensitivity of 99%) to biochemically confirm the diagnosis and CT imaging to localize these tumors. For patients with sporadic disease, surgical resection of the affected gland is the treatment of choice. This resection can frequently be accomplished laparoscopically, although for tumors greater than 6 cm in size, open adrenalectomy is advocated due to the increased risk of malignancy. For patients with hereditary forms of the disease, the authors perform cortical-sparing procedures in an attempt to minimize the patient’s dependence on corticosteroid replacement.

For patients with malignant disease, surgical therapy is indicated in the form of resection for cure or debulking for palliation. Chemotherapy remains disappointing, emphasizing the need for further investigation into targeted therapies.

**References**


