Published in final edited form as:

Eur Urol Focus. 2016 February ; 1(3): 231–240. doi:10.1016/j.euf.2015.09.011.

Pheochromocytoma in Urologic Practice

Nikhil Waingankar¹, Gennady Bratslavsky², Camilo Jimenez³, Paul Russo⁴, and Alexander Kutikov¹

¹ Fox Chase Cancer Center, Philadelphia, Pennsylvania

² SUNY Upstate Medical University, Syracuse, New York

³ The University of Texas MD Anderson Cancer Center, Houston, Texas

⁴ Memorial Sloan Kettering Cancer Center, New York, New York

Abstract

Context—Pheochromocytoma is regularly encountered in urological practice and requires a thoughtful and careful clinical approach.

Objective—To review clinical aspects of management of pheochromocytoma in urologic practice.

Evidence Acquisition—A systematic review of English-language literature was performed through year 2015 using the Medline database. Manuscripts were selected with consensus of the coauthors and evaluated using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria.

Evidence Synthesis—Findings and recommendations of the evaluated manuscripts are discussed with an emphasis on the description of presentation, diagnosis, evaluation, and perioperative care.

Conclusion—In addition to surgical expertise, appropriate management of pheochromocytoma in urologic practice requires nuanced understanding of pathophysiology, genetics, and endocrinological principles. When skillfully managed, the vast majority of patients with pheochromocytoma should expect an excellent prognosis.

Patient Summary—In this article we review the clinical approach to patients with pheochromocytoma, a tumor that stems from the innermost part of the adrenal gland and that often secretes excessive amounts of powerful hormones such as noradrenaline and adrenaline. Significant expertise is required to appropriately manage patients with these tumors.

Take Home Message—In addition to surgical expertise, appropriate management of pheochromocytoma in urologic practice requires nuanced understanding of pathophysiology, genetics, and endocrinological principles. When skillfully managed, vast majority of patients with pheochromocytoma should expect an excellent prognosis.

Keywords

Adrenal; Pheochromocytoma; Blockade; Adrenalectomy; catecholamines metanephrines hypertension

Introduction

The urologic surgeon's intimate knowledge of retroperitoneal anatomy and advanced skillset in both open and minimally-invasive retroperitoneal surgery ideally positions him/her to be a key member of the multidisciplinary team that cares for patients with pheochromocytoma. Nevertheless, beyond technical skill, care of patients with this complex condition requires nuanced expertise in patient evaluation, selection, and medical management. The goal of this manuscript is to review perioperative care of patients with pheochromocytoma.

Evidence Acquisition

A comprehensive review of the English-language literature was performed to review modern management of pheochromocytoma. This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) criteria [1]. The terms *pheochromocytoma* in combination with adrenal, diagnosis, imaging, perioperative, malignant, or *hereditary* were used to perform a Medline database search through June of 2015. Citations from appropriate manuscripts, prior book chapters written by the authors, and prior reviews were harnessed to identify seminal articles in this space. After exclusion of duplicates, the final list of references was identified with co-author consensus.

Evidence Synthesis

The annual incidence of pheochromocytoma ranges from 2 to 8 cases per one million individuals [2, 3]. Among those with non-essential hypertension, pheochromocytoma is found in 0.1 - 0.6% of patients [4, 5]. Patients with an incidentally discovered adrenal lesion >1cm in diameter will be diagnosed with pheochromocytoma in approximately 4-5% of cases [6, 7]. The average age of diagnosis in non-hereditary cases is approximately 45 years, and occurs in equal proportion in males and females [2, 3, 8].

Historically, pheochromocytoma has been labeled as the “10% tumor,” as it was thought to be 10% bilateral, 10% extra-adrenal, 10% hereditary, 10% pediatric, and 10% malignant [9]. Nevertheless, this axiom of medical education has been challenged as the literature on the subject has matured. For instance, some 25% of cases of pheochromocytoma stem from extra-adrenal tissue [10] and as many as 30% are hereditary [11, 12]. Although it is the most common endocrine secreting tumor in children, pheochromocytoma remains rare in this population, with only approximately 2% of those screened for hypertension harboring this pathology [13].

Finally, malignant pheochromocytoma is rare. Indeed, malignant disease is estimated to have an incidence of 93 cases per 400 million persons and thus occurring in approximately 5% of patients with sporadic disease originating in the adrenal [14]. Meanwhile, malignancy is

reported in up to 70% among those with extra-adrenal tumors, and up to 50% of those with *SDHB* mutations [15-17].

Pathophysiology

Pheochromocytoma and paragangliomas are tumors that stem from cells of the neural crest. Neural crest ultimately develops into the sympathetic paraganglia (including the adrenal medulla and organ of Zuckerkandl) and parasympathetic paraganglia (including the carotid body). Pheochromocytomas and paragangliomas can thus develop at any of these locations extending from the head to the pelvic floor. The vast majority of these tumors stem from the adrenal gland; however, up to 25% occur at extra-adrenal sites and are termed paragangliomas [10, 18].

Chromaffin cells lie in the adrenal medulla and are innervated by preganglionic neurons from T11- L2 sympathetic fibers. The enzyme phenylethanolamine-N-methyl transferase (PNMT) is responsible for the conversion of norepinephrine to epinephrine within the adrenal. PNMT is unique to the adrenal gland, the brain, and the organ of Zuckerkandl. As such, the adrenal medulla secretes the catecholamines norepinephrine (80%), epinephrine (19%), and dopamine (1%) [19].

Catecholamines are metabolized by the enzyme Catechol-O-methyl transferase (COMT), which catalyzes the conversion of norepinephrine to normetanephrine, and epinephrine to metanephrine. Thus, these inactive metabolites of catecholamines, collectively known as metanephrines, are also secreted by the gland [20]. Vanillylmandelic acid (VMA) is a degradation product that is formed by the deamination and subsequent O-methylation and oxidation of norepinephrine and epinephrine via the COMT and monoamine oxidase pathways [21].

In response to sympathetic nerve activity, catecholamines that are stored in presynaptic terminal vesicles are released into circulation for travel to end-organs [21]. The ultimate pathophysiologic effects of pheochromocytomas vary based on proportion of each type of catecholamine released, the effector organ, and the target receptor type (alpha vs beta) and subtype. Thus, pheochromocytomas have a wide range of clinical symptoms. For example, the rare tumors that exhibit a predominance of epinephrine release have primary effect on the beta-2 receptor, resulting in systemic vasodilation and the clinical manifestation of orthostatic hypotension. On the other hand, more commonly, tumors with a predominance of norepinephrine release demonstrate primary activity against the alpha receptor, resulting in vasoconstriction and hypertension [22].

Signs and Symptoms

Signs and symptoms of pheochromocytoma are due to excess catecholamine secretion by the tumor. Patients may present with the triad of episodic headache, sweating, and tachycardia [23, 24], although these symptoms are concomitantly present in only 24% of cases [25]. Approximately half of patients have paroxysmal hypertension, of which 50-60% have sustained hypertension in between episodes. Nevertheless, it is important to note that 5-40% of patients with pheochromocytoma never exhibit episodes of blood pressure elevation [26].

As many as 50% of patients are asymptomatic and are diagnosed incidentally during abdominal imaging [15, 25].

Other possible presenting symptoms of pheochromocytoma include angina pectoris, tremor, blurred vision, constipation, nausea, early satiety, weight loss, and anxiety. Less common signs include facial pallor, hypotension (epinephrine-secreting tumor or reflective of low plasma volume), and hyperglycemia [15, 27]. Rarely, a patient can present with catecholamine induced cardiac stress resulting in “Takotsubo cardiomyopathy;” while this is generally transient and reversed by elimination of the catecholamine source, permanent histologic and pathophysiologic changes can occur in some patients [28]. Hyperglycemia is due to the direct effects of catecholamines both on alpha-2 receptors of pancreatic islet cells (resulting in decreased insulin secretion), and on beta-2 receptors of skeletal muscle (resulting in increased contractility and glycogenolysis). As a rule, signs and symptoms of pheochromocytoma could be fully reversed by catecholamine blockade and surgical extirpation [29].

Diagnosis

Workup for pheochromocytoma is generally prompted by the presence of any of the above signs or symptoms, or by the incidental finding of an adrenal mass on axial imaging. Physicians should have a high level of suspicion in patients with episodic or refractory hypertension, hypertension at a young age especially with new onset of diabetes, and in patients with a family history of pheochromocytoma or other endocrine-based tumors (see section below on Familial Pheochromocytoma). Investigation begins with a thorough history and physical examination and a keen eye toward any of the previously mentioned signs and symptoms. Biochemical evaluation should then be pursued, and can include both plasma and urine studies for catecholamines and metanephrines. Imaging can include computed tomography (CT), Magnetic Resonance Imaging (MRI), and functional scintigraphy.

Laboratory studies

The diagnostic accuracy of each laboratory test depends on whether the tumor is sporadic or hereditary. **Table 1** includes sensitivities and specificities for the various laboratory tests. Catecholamine testing is generally not as accurate in diagnosing pheochromocytoma, and has largely been either replaced by or utilized as an adjunct test alongside testing for metanephrines, which carries a sensitivity of 99% and specificity of 89% [30, 31]. This is largely due to the fact that catecholamines are sporadically released into the bloodstream, rendering laboratory evaluation time-dependent. Metanephrine level measurement is more accurate as it is based on the constant adrenal activity of COMT, which converts catecholamines to metanephrines [32].

Urinary VMA levels exhibit inconsistent elevation in the setting of pheochromocytoma compared to that of metanephrines, and accordingly, the sensitivity of VMA testing is low. However, because conversion of catecholamines to VMA occurs through both the COMT and the MAO pathways, VMA testing exhibits high specificity for the diagnosis of pheochromocytoma [30].

Chromogranin A and Neuropeptide Y levels are elevated in 80% and 87% of patients with pheochromocytoma, respectively [33, 34]. However, given the superb diagnostic accuracy of metanephrine-testing, along with the dependence of Chromogranin A and Neuropeptide Y testing on normal renal function, routine testing for the latter has never gained clinical traction.

Clonidine suppression is a test that is occasionally used to differentiate pheochromocytoma from essential hypertension and can aid in diagnostic confirmation when traditional means produce equivocal results. Clonidine is a centrally acting alpha-2 agonist that suppresses catecholamine release in the healthy state, but not in patients with pheochromocytoma. A 0.3mg dose is administered orally, and plasma catecholamines and fractionated metanephrines are measured before and 3 hours after. Patients with essential hypertension should demonstrate a 50% decrease in norepinephrine and 40% decrease in metanephrine levels, whereas those with pheochromocytoma will have persistently elevated levels [35]. Care must be taken in those patients with hypovolemia and non-hypertensive patients as profound hypotension can result.

In urologic practice, the urologist most often tackles a patient with findings of an incidental adrenal mass. The Endocrine Society 2014 clinical practice guidelines recommend plasma free or urinary fractionated metanephrines for initial biochemical testing [30, 31]. **Figure 1** shows an example of a clinical prescription that can be used to facilitate evaluation of a patient with adrenal mass. Plasma-free (fractionated) metanephrine testing is extremely convenient as this test can be obtained on the same blood draw as hypercortisolemia and hyperaldosteronism interrogation. It is important to note that tricyclic antidepressants and phenoxybenzamine should be stopped prior to metanephrine testing. Historically, patients were instructed to stop taking acetaminophen 5 days prior to plasma free metanephrine testing, as the compound cross-reacted with the assay and caused false positive results [36]. Current assays are no longer affected by acetaminophen use [37]. Although beta-blockers can be responsible for false-positive results, in general, antihypertensive therapy can remain in place, and is only withdrawn for confirmatory testing in the event of a positive test result [36].

Imaging Studies

Non-contrast CT scan and MRI have similar accuracy in characterizing pheochromocytoma, with sensitivity ranging 93-98% for adrenal-only disease [10]. Cross-section adrenal imaging pivots on quantification of intracellular lipid. Save for isolated case reports [38], adrenal pheochromocytoma are lipid poor and thus can be readily differentiated from vast majority of adrenal adenomas. CT findings suggestive of pheochromocytoma include high attenuation on noncontrast CT (> 10 Hounsfield Units (HU) and often > 25 HU). Lack of signal dropout on out-of-phase sequences on chemical-shift MRI (this does not require Gadolinium-based contrast) also signifies a lipid-poor lesion. A lesion that demonstrates low attenuation (< 10 HU) on non-contrast CT or shows signal dropout on MRI is nearly always a benign adenoma. Nevertheless, 30% of adenomas can exhibit lipid-poor features and can be differentiated from pheochromocytoma on CT washout studies where loss of iodinated contrast within a lesion is quantified. Unlike adenomas, pheochromocytomas demonstrate

sluggish contrast washout at both 10 and 15 minutes following contrast administration [39]. Despite the ability of cross-sectional imaging to differentiate pheochromocytoma from adenoma, differentiating pheochromocytoma from other lipid poor lesions such as adrenocortical carcinoma or metastases largely pivots on the metabolic work-up. The classic MRI finding of a “light bulb sign,” or increased signal intensity on T2 imaging, is no longer considered pathognomonic, since up to 35% of cases can be misclassified [40]. Other imaging hallmarks of pheochromocytoma may include prominent mass vascularity, occasional findings of hemorrhage, cystic components, and the slow growth rate of 0.5-1cm per year (**Figure 2, Table 2**) [39, 41].

Functional imaging provides limited incremental benefit in patients with biochemical testing and CT or MRI, aiding in localization of 1.4% of primary cases and 3.5%) of cases with metastases [42]. Metaiodobenzylguanidine (MIBG) is a substrate of the catecholamine transporter that can be radiolabeled (^{123}I or ^{131}I) and is taken up by adrenergic tissue. When paired with the anatomic detail afforded by CT scan, ^{123}I MIBG has sensitivity ranging 83-100% and specificity of 95-100% [10]. While the role of MIBG scanning in localized adrenal pheochromocytoma is debated, it may be useful in ruling out metastatic pheochromocytoma, and/or differentiating between metastatic pheochromocytoma vs. adrenal cortical cancer in patients with large primary lesions >5cm [10, 15].

Fluorodeoxyglucose Positron Emission Tomography (^{18}F -FDG PET) possesses impressive test characteristics in staging patients with metastatic and multifocal *SDHx*-related pheochromocytoma, [43]. For patients with Multiple Endocrine Neoplasia Type 2 (MEN2), however, MIBG remains the superior test, as ^{18}F -FDG PET exhibits low sensitivity (<50%) in this patient population.

Radiolabeled Gallium DOTA-1-NaI(3)-octreotide (^{68}Ga -DOTANOC) is an alternative functional study that targets pheochromocytoma's somatostatin receptors. This radiographic modality demonstrates a higher diagnostic accuracy than ^{131}I -MIBG. Indeed, impressive 100% accuracy in patients with multiple endocrine neoplasia 2 (MEN2) syndrome and malignant pheochromocytoma has been reported [44]. ^{111}In -pentetreotide scintigraphy (Octreoscan) has been utilized at some institutions but has poor sensitivity and specificity compared with the other forms of functional imaging [45].

Treatment

The treatment of pheochromocytoma is surgical extirpation. The surgical and anesthesia teams must be vigilant to avoid catecholamine surge, which can be caused by manipulation of the tumor during surgery, intubation, abdominal insufflation, and the use of intraoperative pharmacologic agents (opiates, neuromuscular blockers, sympatricomimetics, vagolytics, and tranquilizers). Potential sequelae of catecholamine surge include hypertensive crisis, cardiac arrhythmias, heart attacks, strokes, and death. Thus, preoperative optimization should be managed on a multidisciplinary basis between the surgeon, endocrinologist, and anesthesiologist. The primary goals of optimization are: 1) Control of hypertension, 2) Avoidance of arrhythmias, and 3) Maintenance of intravascular volume.

Preoperative Preparation

There is no consensus on the optimal strategy for preoperative management of a patient with biochemically confirmed pheochromocytoma. Commonly utilized strategies include alpha blockade as first line treatment with the addition of beta blockade for patients once they develop a reflex tachycardia or orthostatic hypotension; catecholamine synthesis blockade; and calcium channel blockade in patients with persistently poorly controlled hypertension. Alternatively, other institutions preferentially initiate treatment with calcium channel blockade followed by catecholamine synthesis blockade (**Figure 3**). Regardless of the pharmacologic intervention, all patients should be adequately hydrated preoperatively; some institutions routinely preadmit patients for IV fluids before surgery [22, 38].

Preliminary data from some centers suggest that asymptomatic patients who do not exhibit hypertension or hypertensive episodes may be spared perioperative blockade and indeed may be less likely to receive intraoperative vasoactive agent administration. Nevertheless, these initial reports require validation, and extreme caution must be exercised, since asymptomatic patients can still exhibit a clinically significant intraoperative catecholamine surge [46].

Alpha Blockade

Phenoxybenzamine, an irreversible antagonist of the alpha-receptor, is a commonly utilized alpha-blocker for management of hypertension associated with pheochromocytoma. The typical starting dose is 10mg by mouth twice daily, and the agent is titrated to higher doses until hypertension is controlled. Adverse drug reactions are generally related to high doses, and include hypotension, reflex tachycardia, dizziness, and syncope. Postoperatively, patients may be hypotensive due to the loss of the catecholamine source and the irreversible blockade of the alpha receptors. Because of this undesired effect, many institutions advocate the use of alpha-1 antagonists such as doxazosin, terazosin, or prazosin due to their short duration of action as a complete replacement to phenoxybenzamine [22].

Beta Blockade

Alpha blockers should first be initiated to control hypertension, with beta blockers added only in the setting of catecholamine- or antihypertensive-induced tachycardia. Beta blockers should never be used as first line therapy, as they can predispose to hypertension caused by catecholamines via impairment of their vasodilatory effect of beta-2 receptors in the skeletal muscle vascular bed [22]. Selective (Metoprolol, Atenolol, etc) and non-selective beta blockers (propranolol) can be used to prevent toxicity on beta receptors.

Labetalol is a dual alpha- and beta- antagonist that has been used in some institutions as presurgical monotherapy. Caution should be taken, as labetalol carries a 1:7 alpha:beta antagonist ratio, and the desired balance is closer to 4:1 favoring alpha blockade [47]. Its use could then lead to the untoward effect of excess epinephrine-induced vasoconstriction due to inhibited peripheral beta-2 mediated vasodilatation. Moreover, if labetalol is used, it should be stopped 2 weeks prior to ¹³¹I-MIBG scan as it can inhibit its uptake [22].

Calcium Channel Blockade

Medications such as amlodipine, nicardipine, and nifedipine inhibit the norepinephrine-mediated influx of calcium into vascular smooth muscle cells, which can control both hypertension and tachyarrhythmias. Thus, calcium channel blockers have been used as monotherapy in some institutions. Advocates of this strategy suggest that, like alpha-1 antagonists, calcium channel blockers don't cause irreversible blockade and persistent postoperative hypotension that can be associated with phenoxybenzamine following adrenalectomy. Other institutions use calcium channel blockers as adjunctive therapy to alpha blockade in patients with inadequately controlled blood pressure, or in those with intolerable adverse drug reactions to alpha blockade [22, 38, 48].

Catecholamine Synthesis Blockade

Alpha-methyl-L-tyrosine (metyrosine) is a tyrosine analog that inhibits tyrosine hydroxylase, and thus prevents the conversion of tyrosine to L-DOPA, the rate limiting step in catecholamine synthesis [22]. Because metyrosine takes 3 days to reach its full effect, and because it results in incomplete blockade, institutions that advocate use of catecholamine synthesis blockade use this in tandem with alpha- or calcium-channel blockade. Some have noted improved intraoperative blood pressure control with this combined strategy [49]. In the recent years, obtaining metyrosine in the United States has been challenging due to supply shortages and cost. Many centers of excellence do not prescribe it as side effects are difficult to tolerate (anxiety, depression, fatigue, and diarrhea).

In traoperative Management

Central venous catheter and arterial pressure monitoring are standard at many institutions for intra- and post-operative monitoring [50]. Intraoperatively, acute rises in blood pressure in patients with pheochromocytoma can result from induction of general anesthesia and endotracheal intubation, mechanical ventilation changes, patient positioning, establishment of pneumoperitoneum, and surgical manipulation of the tumor. Increasing the depths of anesthesia and paralysis can minimize these fluctuations. Furthermore, vasoactive agent administration and titration is essential to maintaining a hemodynamically stable patient. In addition to alpha- and calcium channel blockade, commonly used agents include Nicardipine, sodium nitroprusside, nitroglycerine, phentolamine, magnesium sulfate, and urapidil; esmolol is used as a beta1-blocker to control and prevent tachyarrhythmias and coronary events. Magnesium is unique because it exerts a direct vasodilatory effect on peripheral vasculature, inhibits catecholamine release from the adrenal medulla and adrenergic nerve terminals, and directly blocks peripheral catecholamine receptors [51]. However, it predisposes to hypermagnesemia and prolonged paralysis. In this scenario, nicardipine is perhaps, the best option.

Surgically, open and minimally invasive techniques (trans and retroperitoneal), including laparoscopy and robotics, are well-described and acceptable approaches to adrenal pheochromocytoma resection. The primary principles of extirpative adrenal surgery in the setting of pheochromocytoma are, 1) avoidance of excess tumor manipulation, and 2) attempt at early ligation of the adrenal vein. Open communication between the surgical and anesthesia teams is essential to the success of these often complex operations.

Partial adrenalectomy is an option for select patients, and is gaining significant traction for patients with hereditary pheochromocytoma when feasible [52, 53]. Prior studies have shown that adrenal preservation is not only possible in patients with pheochromocytoma, but it also allows for excellent long-term functional and oncologic outcomes. Benhamou and associates studied outcomes of patients with Von Hippel-Lindau (VHL) and pheochromocytoma who were treated with partial adrenalectomy and had at least 5 years of follow up. Recurrence rate was less than 10% and most avoided glucocorticoid replacement therapy [52]. Recent review by Kaye and colleagues identified that the utilization of adrenal-sparing surgery is increasing worldwide for all types of small adrenal masses. Nevertheless, because of a higher likelihood for bilaterality and genetic causes, the optimal management of adrenal pheochromocytoma in all-comers should consider adrenal preservation when technically feasible [54]. For patients with bilateral adrenal pheochromocytomas, a staged approach is recommended; moreover, intervention should take place before the tumors reach 4cm to allow for the best functional outcomes [55]. Partial adrenalectomy can be performed using pure laparoscopy or with robotic assistance [53, 56], and results in reasonable outcomes even in those patients with a solitary adrenal gland [57].

Postoperative Management

In patients who received phenoxybenzamine, the irreversible alpha blockade can contribute to hypotension in the first 24 hours or longer (half-life is 10 days) after tumor removal, and thus, fluid resuscitation becomes paramount. Immediate postoperative stay in an intensive care setting is standard in many institutions, as close postoperative hemodynamic monitoring is necessary. Hypoglycemia is a rare but possible finding in the postoperative state. Pheo-induced stimulation of the alpha-2 receptor can inhibit insulin release leading to hyperglycemia. Discontinuation of this stimulus can result in hyperinsulinemia and hypoglycemia.

Long-term follow-up of pheochromocytoma patients with hereditary predisposition and/or clinical predictors for recurrent or metastatic disease to evaluate for recurrent or metastatic disease is currently recommended [17], since cases of systemic progression as far as 40 years following initial resection has been reported. As such, at least annual biochemical testing with plasma or urine metanephrines and periodic conventional radiographic studies is prudent, once post-surgical metanephrine normalization has been documented [17, 58-61].

Special Considerations

Malignant Pheochromocytoma

Malignant pheochromocytomas are histologically and biochemically similar to benign cases, and while pathologic criteria exist, none accurately diagnose malignant pheochromocytoma [62]. Malignancy is characterized as the presence of metastases. Larger tumor size, sympathetic paragangliomas (rather than pheochromocytomas stemming from adrenal gland), and succinate dehydrogenase B (*SDHB*) mutations are associated with decreased overall survival as these clinical characteristics are associated with a higher risk of metastases[17].

Medical treatment of malignant pheochromocytoma necessitates biochemical blockade, and management is largely palliative [58]. Chemotherapy is used for patients who have rapidly progressive and/or symptomatic disease [63]. The most commonly used chemotherapy regimen is cyclophosphamide, vincristine, and dacarbazine, which has demonstrated a partial response rate of 25-55%, and a biochemical response rate of 47% [58]. The difficulty in justifying its use as first line therapy is the tradeoff of its significant toxicities for a non-durable response of 21-22 months [61]. However, those who respond to chemotherapy (improved blood pressure control and tumor size reduction when compared with baseline) have retrospectively been associated with a survival advantage over those with no response [63]. MIBG therapy is utilized in some centers for patients with malignant pheochromocytoma and paragangliomas; a recent meta-analysis demonstrates stable disease and partial hormonal response in up to 50% of patients; nevertheless these results may be explained in part due the natural history of the disease; in fact, many of these patients had stable rather than progressive disease before treatment was provided [64]. So far, MIBG therapy has not been associated with survival benefits. Sunitinib is a multityrosine kinase inhibitor that has been used to treat patients with malignant tumors. In a retrospective intention-to-treat study, 47% of patients exhibited partial radiographic responses, stable disease, decreased glucose uptake, and blood pressure control; these benefits were noted in patients with sporadic, SDHB, and VHL metastatic tumors [59, 65]. There are currently three active prospective clinical trials (sunitinib and cabozantinib) evaluating the actions of these molecular targeted therapies in patients with malignant disease (www.ClinicalTrials.Gov).

Finally, surgical resection remains an option for palliative symptom control, although there is no robust evidence to suggest that metastasectomy or removal of the primary tumor have better outcomes than medical management [15].

Hereditary Pheochromocytoma

Hereditary pheochromocytoma should be considered in every patient, especially if the tumor is diagnosed before age 50, and in those with bilateral, multifocal, and/or extra-adrenal disease. There are 12 genes that are associated with familial pheochromocytoma and paraganglioma: VHL, RET, NF1, SDHA, SDHC, SDHD, SDHB, TMEM127, MAX, FH, malate dehydrogenase, and EPAS 1.

VHL involves an autosomal dominant mutation of chromosome 3p and is commonly seen in urologic practice due to the propensity of these patients to develop renal cell carcinoma. Other stigmata seen in VHL include central nervous system and retinal hemangioblastomas, pancreatic cysts and neuroendocrine tumors, epididymal cystadenomas, and endolymphatic sac tumors.

MEN 2a and 2b involve autosomal dominant mutations of chromosome 10q resulting in a defective tyrosine kinase receptor (RET). Aside from pheochromocytoma, MEN 2a patients can harbor medullary thyroid cancer, primary hyperparathyroidism, and cutaneous lichen amyloidosis, while those afflicted with MEN 2b are at risk for medullary thyroid cancer, neuromas, and Marfanoid body habitus.

Neurofibromatosis Type 1 (NF1) is caused by an autosomal dominant mutation of the NF1 gene on 17q. Identifiable characteristics include café au lait skin lesions, neurofibromas, and acoustic schwannomas.

Finally, familial paraganglioma syndromes type 1 (*SDHD* mutation on 11q; maternal imprinting) and type 4 (*SDHB* mutation on 1p; autosomal dominant) are associated with pheochromocytomas, and sympathetic and parasympathetic paragangliomas [12, 15]. As mentioned previously, those patients with mutations of the *SDHB* gene carry a significantly higher risk of malignant disease.

Again, partial adrenalectomy should be considered in patients at risk for bilateral or multiple lesions [52, 57], and all patients should be counseled that steroid hormone replacement may ultimately be necessary [38].

Conclusions

Due to his/her familiarity with retroperitoneal anatomy and expertise in minimally invasive surgical techniques, the urologist is ideally positioned to manage patients with pheochromocytoma. Nevertheless, nuanced understanding of not only surgical but also medical pheochromocytoma management is mandatory to appropriately manage these complex patients who stand to greatly benefit from well-executed surgical extirpation.

Acknowledgments

Dr. Paul Russo received support through the NIH/NCI Cancer Center Support Grant P30 CA008748.

References

1. Liberati A, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med.* 2009; 151(4):W65–94. [PubMed: 19622512]
2. Beard CM, et al. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc.* 1983; 58(12):802–4. [PubMed: 6645626]
3. Stenstrom G, Svarsdudd K. Pheochromocytoma in Sweden 1958-1981. An analysis of the National Cancer Registry Data. *Acta Med Scand.* 1986; 220(3):225–32. [PubMed: 3776697]
4. Sinclair AM, et al. Secondary hypertension in a blood pressure clinic. *Arch Intern Med.* 1987; 147(7):1289–93. [PubMed: 3606286]
5. Omura M, et al. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. *Hypertens Res.* 2004; 27(3):193–202. [PubMed: 15080378]
6. Young WF Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. *Endocrinol Metab Clin North Am.* 2000; 29(1):159–85. x. [PubMed: 10732270]
7. Mantero F, et al. A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. *J Clin Endocrinol Metab.* 2000; 85(2):637–44. [PubMed: 10690869]
8. Amar L, et al. Genetic testing in pheochromocytoma or functional paraganglioma. *J Clin Oncol.* 2005; 23(34):8812–8. [PubMed: 16314641]
9. Scott, WH.; V.W.C.; Gray, GF.; Sussman, CR. *Surgery of the adrenal glands.* JB Lippincott; Philadelphia: 1990. Pheochromocytoma.; p. 187-223.
10. Ilias I, Pacak K. Current approaches and recommended algorithm for the diagnostic localization of pheochromocytoma. *J Clin Endocrinol Metab.* 2004; 89(2):479–91. [PubMed: 14764749]

11. Neumann HP, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med.* 2002; 346(19):1459–66. [PubMed: 12000816]
12. Dluhy RG. Pheochromocytoma--death of an axiom. *N Engl J Med.* 2002; 346(19):1486–8. [PubMed: 12000821]
13. Beltsevich DG, et al. Pheochromocytoma surgery: epidemiologic peculiarities in children. *World J Surg.* 2004; 28(6):592–6. [PubMed: 15366751]
14. Parenti G, et al. Updated and new perspectives on diagnosis, prognosis, and therapy of malignant pheochromocytoma/paraganglioma. *J Oncol.* 2012; 2012:872713. [PubMed: 22851969]
15. Lenders JW, et al. Phaeochromocytoma. *Lancet.* 2005; 366(9486):665–75. [PubMed: 16112304]
16. Whalen RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. *J Urol.* 1992; 147(1):1–10. [PubMed: 1729490]
17. Ayala-Ramirez M, et al. Clinical risk factors for malignancy and overall survival in patients with pheochromocytomas and sympathetic paragangliomas: primary tumor size and primary tumor location as prognostic indicators. *J Clin Endocrinol Metab.* 2011; 96(3):717–25. [PubMed: 21190975]
18. DeLellis, RA.; L.R.; Heitz, PU., et al. Pathology and Genetics of Tumours of Endocrine Organs.. In: Lyon, F., editor. World Health Organization classification of tumours. Vol. 8. IARC Press; 2004.
19. Robertson, D.; Scott, WH. Surgery of the adrenal glands. Lippincott; Philadelphia: 1990. The adrenal medulla and adrenomedullary hormones..
20. de Diego AM, Gandia L, Garcia AG. A physiological view of the central and peripheral mechanisms that regulate the release of catecholamines at the adrenal medulla. *Acta Physiol (Oxf).* 2008; 192(2):287–301. [PubMed: 18005392]
21. Eisenhofer G, Kopin IJ, Goldstein DS. Catecholamine metabolism: a contemporary view with implications for physiology and medicine. *Pharmacol Rev.* 2004; 56(3):331–49. [PubMed: 15317907]
22. Pacak K. Preoperative management of the pheochromocytoma patient. *J Clin Endocrinol Metab.* 2007; 92(11):4069–79. [PubMed: 17989126]
23. Bravo EL. Pheochromocytoma: new concepts and future trends. *Kidney Int.* 1991; 40(3):544–56. [PubMed: 1787652]
24. Stein PP, Black HR. A simplified diagnostic approach to pheochromocytoma. A review of the literature and report of one institution's experience. *Medicine (Baltimore).* 1991; 70(1):46–66. [PubMed: 1988766]
25. Baguet JP, et al. Circumstances of discovery of phaeochromocytoma: a retrospective study of 41 consecutive patients. *Eur J Endocrinol.* 2004; 150(5):681–6. [PubMed: 15132724]
26. Manger WM, Gifford RW. Pheochromocytoma. *J Clin Hypertens (Greenwich).* 2002; 4(1):62–72. [PubMed: 11821644]
27. Thosani S, et al. Constipation: An Overlooked, Unmanaged Symptom of Patients with Pheochromocytoma and Sympathetic Paraganglioma. *Eur J Endocrinol.* 2015
28. Kassim TA, et al. Catecholamine-induced cardiomyopathy. *Endocr Pract.* 2008; 14(9):1137–49. [PubMed: 19158054]
29. Stenstrom G, Sjostrom L, Smith U. Diabetes mellitus in phaeochromocytoma. Fasting blood glucose levels before and after surgery in 60 patients with phaeochromocytoma. *Acta Endocrinol (Copenh).* 1984; 106(4):511–5. [PubMed: 6475457]
30. Lenders JW, et al. Biochemical diagnosis of pheochromocytoma: which test is best? *JAMA.* 2002; 287(11):1427–34. [PubMed: 11903030]
31. Lenders JW, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014; 99(6):1915–42. [PubMed: 24893135]
32. Eisenhofer G, et al. Pheochromocytoma: rediscovery as a catecholamine-metabolizing tumor. *Endocr Pathol.* 2003; 14(3):193–212. [PubMed: 14586065]
33. Cotesta D, et al. High plasma levels of human chromogranin A and adrenomedullin in patients with pheochromocytoma. *Tumori.* 2005; 91(1):53–8. [PubMed: 15850005]

34. Mouri T, et al. Neuropeptide Y as a plasma marker for pheochromocytoma, ganglioneuroblastoma and neuroblastoma. *Clin Sci (Lond)*. 1992; 83(2):205–11. [PubMed: 1327637]
35. Sjöberg RJ, Simicic KJ, Kidd GS. The clonidine suppression test for pheochromocytoma. A review of its utility and pitfalls. *Arch Intern Med*. 1992; 152(6):1193–7. [PubMed: 1599347]
36. Eisenhofer G, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. *J Clin Endocrinol Metab*. 2003; 88(6):2656–66. [PubMed: 12788870]
37. Roden M, et al. Quantification of unconjugated metanephrines in human plasma without interference by acetaminophen. *Clin Chem*. 2001; 47(6):1061–7. [PubMed: 11375292]
38. Kutikov, A.; Cripsen, PL.; Uzzo, RG. Pathophysiology, Evaluation, and Medical Management of Adrenal Disorders.. In: Wein; Kavoussi; Novick; Partin; Peters, editors. *Campbell-Walsh Urology*. Vol. 2. Elsevier; 2012. p. 1685-1736.
39. Kutikov, A. Disorders of the Adrenal Gland.. In: Hanno PM, GT.; Malkowicz, SB.; Wein, AJ., editors. *Penn Clinical Manual of Urology*. 2nd ed.. Elsevier; 2014. p. 769-788.
40. Varghese JC, et al. MR differentiation of pheochromocytoma from other adrenal lesions based on qualitative analysis of T2 relaxation times. *Clin Radiol*. 1997; 52(8):603–6. [PubMed: 9285420]
41. Young WF Jr. Clinical practice. The incidentally discovered adrenal mass. *N Engl J Med*. 2007; 356(6):601–10. [PubMed: 17287480]
42. Brito JP, et al. The incremental benefit of functional imaging in pheochromocytoma/paraganglioma: a systematic review. *Endocrine*. 2015
43. Timmers HJ, et al. Staging and functional characterization of pheochromocytoma and paraganglioma by 18F-fluorodeoxyglucose (18F-FDG) positron emission tomography. *J Natl Cancer Inst*. 2012; 104(9):700–8. [PubMed: 22517990]
44. Sharma P, et al. Diagnostic accuracy of (68)Ga-DOTANOC PET/CT imaging in pheochromocytoma. *Eur J Nucl Med Mol Imaging*. 2014; 41(3):494–504. [PubMed: 24158184]
45. Ilias I, et al. Comparison of 6-18F-fluorodopamine PET with 123I-metaiodobenzylguanidine and 111In-pentetreotide scintigraphy in localization of nonmetastatic and metastatic pheochromocytoma. *J Nucl Med*. 2008; 49(10):1613–9. [PubMed: 18794260]
46. Shao Y, et al. Preoperative alpha blockade for normotensive pheochromocytoma: is it necessary? *J Hypertens*. 2011; 29(12):2429–32. [PubMed: 22025238]
47. Kanto JH. Current status of labetalol, the first alpha- and beta-blocking agent. *Int J Clin Pharmacol Ther Toxicol*. 1985; 23(11):617–28. [PubMed: 2867049]
48. Ulchaker JC, et al. Successful outcomes in pheochromocytoma surgery in the modern era. *J Urol*. 1999; 161(3):764–7. [PubMed: 10022680]
49. Perry RR, et al. Surgical management of pheochromocytoma with the use of metyrosine. *Ann Surg*. 1990; 212(5):621–8. [PubMed: 1978640]
50. Lentschener C, et al. Point of controversy: perioperative care of patients undergoing pheochromocytoma removal-time for a reappraisal? *Eur J Endocrinol*. 2011; 165(3):365–73. [PubMed: 21646289]
51. Livingstone M, et al. Hemodynamic Stability During Pheochromocytoma Resection: Lessons Learned Over the Last Two Decades. *Ann Surg Oncol*. 2015
52. Benhammou JN, et al. Functional and oncologic outcomes of partial adrenalectomy for pheochromocytoma in patients with von Hippel-Lindau syndrome after at least 5 years of followup. *J Urol*. 2010; 184(5):1855–9. [PubMed: 20846682]
53. Asher KP, et al. Robot-assisted laparoscopic partial adrenalectomy for pheochromocytoma: the National Cancer Institute technique. *Eur Urol*. 2011; 60(1):118–24. [PubMed: 21507561]
54. Kaye DR, et al. Partial adrenalectomy: underused first line therapy for small adrenal tumors. *J Urol*. 2010; 184(1):18–25. [PubMed: 20546805]
55. Sanford TH, et al. Outcomes and timing for intervention of partial adrenalectomy in patients with a solitary adrenal remnant and history of bilateral pheochromocytomas. *BJU Int*. 2011; 107(4):571–5. [PubMed: 20726977]
56. Boris RS, et al. Robot-assisted laparoscopic partial adrenalectomy: initial experience. *Urology*. 2011; 77(4):775–80. [PubMed: 21122898]

57. Gupta GN, et al. Perioperative, functional, and oncologic outcomes of partial adrenalectomy for multiple ipsilateral pheochromocytomas. *J Endourol.* 2014; 28(1):112–6. [PubMed: 23998199]
58. Baudin E, et al. Therapy of endocrine disease: treatment of malignant pheochromocytoma and paraganglioma. *Eur J Endocrinol.* 2014; 171(3):R111–22. [PubMed: 24891137]
59. Jimenez C, et al. Current and future treatments for malignant pheochromocytoma and sympathetic paraganglioma. *Curr Oncol Rep.* 2013; 15(4):356–71. [PubMed: 23674235]
60. Plouin PF, et al. Metastatic pheochromocytoma and paraganglioma: focus on therapeutics. *Horm Metab Res.* 2012; 44(5):390–9. [PubMed: 22314389]
61. Scholz T, et al. Clinical review: Current treatment of malignant pheochromocytoma. *J Clin Endocrinol Metab.* 2007; 92(4):1217–25. [PubMed: 17284633]
62. Wu D, et al. Observer variation in the application of the Pheochromocytoma of the Adrenal Gland Scaled Score. *Am J Surg Pathol.* 2009; 33(4):599–608. [PubMed: 19145205]
63. Ayala-Ramirez M, et al. Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas: insights from the largest single-institutional experience. *Cancer.* 2012; 118(11):2804–12. [PubMed: 22006217]
64. van Hulsteijn LT, et al. (131)I-MIBG therapy for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf).* 2014; 80(4):487–501. [PubMed: 24118038]
65. Ayala-Ramirez M, et al. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. *J Clin Endocrinol Metab.* 2012; 97(11):4040–50. [PubMed: 22965939]

NAME _____ DATE _____

ADDRESS _____ AGE _____

R Nothing to eat or drink after midnight the night prior to blood work.
Blood work to be drawn before 9:30 am.

- ☒ Morning serum cortisol level (patient to have taken 1 mg of dexamethasone at 11 pm the night prior; patient cannot be on oral contraceptives)
- ☒ Morning serum aldosterone and renin level (to be drawn in sitting position)
- ☒ Morning plasma free metanephrines (no caffeine for 24 hours, no Tylenol for 5 days, to be drawn with patient in supine position)
- ☐ 24-hour urine collection for cortisol level, creatinine level (patient must have normal renal function)
- ☐ 24-hour urine collection for metanephrine level, creatinine level (patient must have normal renal function)
- ☐ DHEA-S, 17-OH-progesterone, Androstenedione, Testosterone, 17B-estradiol

_____, M.D.

Figure 1.

A standardized prescription used in the clinical setting for metabolic evaluation of patients with adrenal incidentaloma. Plasma free metanephrines can be drawn at the same early morning blood draw as laboratory tests to evaluate hypercortisolemia and hyperaldosteronism.

Figure 2.

Computed Tomography Scan of Abdomen/Pelvis of a 59 y.o. male with weight loss and fatigue whose plasma-free metanephrines measured 2306 pg/mL (ref range <206 pg/mL). A) Noncontrast CT phase underscores lipid poor nature of pheochromocytoma (attenuation of 30 HU). B) 1 min post-IV contrast phase demonstrating significant mass vascularity with surrounding varicosities (block arrow). C) Coronal image demonstrating central necrosis (notched arrow), and displacement of the ipsilateral renal unit.

Figure 3.

Preoperative medical management algorithms (Adapted from [22, 38]). Doxazosin (1-20mg po daily) and Terazosin (1-20mg po daily) are alternatives to phenoxybenzamine in Option 1.

Table 1

Test characteristics for biochemical evaluation of Pheochromocytoma (Adapted from[30, 38])

	Sensitivity		Specificity	
	Hereditary	Sporadic	Hereditary	Sporadic
Plasma-free Metanephrines	97%	99%	96%	82%
Plasma Catecholamines	69%	92%	89%	72%
Urinary-Fractionated Metanephrines	96%	97%	82%	45%
Urinary Catecholamines	79%	91%	96%	75%
Urinary Total Metanephrines	60%	88%	97%	89%
Urinary Vanillylmandelic Acid	46%	77%	99%	86%

Table 2

Imaging Characteristics of Adrenal Lesions (Adapted from [39])

Adrenal Pathology	Malignant Potential	Incidence	Metabolic Activity	Radiographic Characteristics	Treatment
Pheochromocytoma	93 cases per 400 million (higher in extra-adrenal)	2 cases per one million	Excess catecholamines best tested by plasma metanephrine levels	>10HFU on noncon CT, little contrast washout at 15 min on contrast CT; No signal dropout on in/out phase MRI	Preop blockade, surgery
Ganglioneuroma	Benign	Rare	None	<40HFU on noncontrast CT; stippled calcifications	Dx made upon resection
Cysts	7% associated with malignancy; otherwise benign	0.1% on autopsy series	None	Nonenhancing	Resection vs. observation
Adrenocortical Carcinoma	Malignant	2 cases per one million	50% nonfunctional; hypercortisolism most common; Virilization in up to 10%, feminization in 20%; hyperaldo < 5%	Mean HFU on noncontrast CT = 39, no washout at 15 min on contrast CT; No dropout on in/out phase MRI	Resection, adjuvant mitotane, chemotherapy
Adenoma	Benign	6% on autopsy	6% hypercortisolism, 1% hyperaldo	Mean HFU on noncontrast CT = 8, 95% washout at 15 min on contrast CT; 70% signal dropout on in/out phase MRI	Resection if metabolically active or large (>4-6cm)
Myelolipoma	Benign	0.10%	None	Macroscopic lipid on CT/MRI	None