Pheochromocytoma and Paragangliomas
Current Management Strategies

Reuben Ben-David, MD*, Ahmed Eraky, MD, Reza Mehrazin, MD, Nikhil Waingankar, MD

KEYWORDS

• Pheochromocytoma • Paraganglioma • Neuroendocrine tumors
• Extra-adrenal pheochromocytoma • Adrenal pheochromocytoma

KEY POINTS

- Pheochromocytomas (PCC) and paragangliomas (PGL) are rare neuroendocrine tumors and 15-20% of cases may present with or develop metastatic disease. Hereditary germline mutations are identified in 40% of patients.
- Biochemical testing remains the cornerstone of disease diagnosis. Plasma-free metanephrines measured by liquid chromatography-tandem mass spectrometry provide the most reliable diagnosis for PCC/PGL. Clinicians must be familiar with factors that could cause false positives.
- Computed tomographic (CT) and MRI scans are standard for anatomic localization of PCC and PGLs, but functional imaging using PET/CT with novel radiotracers (ie, 68 Gallium dodecanetetraacetic acid (DOTA) and Tyr3-octreotate (TATE) [^{68}Ga-DOTATATE]) has proven superior for detecting metastatic or multifocal disease, especially in patients with hereditary germline mutations.
- Surgical management remains the gold standard for localized PCC/PGL. Minimally invasive approaches have reduced morbidity and convalescence. Yet, open surgery remains the standard of care for large complex tumors.
- Advancement in the care of metastatic disease includes radioligand therapy, oral tyrosine kinase inhibitors, and receptor radionuclide therapy, though accessibility worldwide and efficacy vary.

INTRODUCTION

Pheochromocytomas (PCC) and paragangliomas (PGL) are rare tumors of neuroendocrine origin, arising from chromaffin cells.[1] In physiologic conditions, chromaffin cells are regulated by the autonomic nervous system and are responsible for the production of catecholamines. These cells are predominantly located in the adrenal medulla and the sympathetic paraganglia. Outside the adrenal medulla, the largest collection of these cells is in the organ of Zuckerkandl—a chain of paraganglia situated around the inferior mesenteric artery and the aortic bifurcation.[1,2] Tumors originating from the adrenal medulla are classified as PCC, while those arising from extra-adrenal autonomic paraganglia are termed PGL. Although both PCC and PGL are typically benign and are detected in the localized stage, a subset of 15% to 20% of patients may present with de novo metastatic disease or develop metastatic recurrence following primary curative treatment. In addition, hereditary germline mutations are commonly identified in 30% to 40% of patients with PCC/PGL.[3]

PCC and PGL are derived from metabolically active cells that secrete catecholamines, leading

Department of Urology, Icahn School of Medicine at Mount Sinai, 1 Gustave L Levy Pl, New York, NY 10029, USA
* Corresponding author. 1425 Madison Avenue, New York, NY 10029.
E-mail address: reuben.bendavid@mountsinai.org

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Abbreviations

CI	confidence interval
CT	computed tomography
HIF	hypoxia-inducible factor
HU	Hounsfield units
LC-MS/MS	liquid chromatography-tandem mass spectrometry
MEN-2	multiple endocrine neoplasia 2
NCCN	National Comprehensive Cancer Network
PCC	pheochromocytomas
PGL	paragangliomas
SDHx	succinate dehydrogenase
SSTRs	somatostatin receptors
TKI	tyrosine kinase inhibitor
VMA	vanillylmandelic acid

to catecholamine overproduction and a broad spectrum of clinical manifestations. Historically, a classic triad of symptoms—headaches, palpitations, and profuse sweating—has been described. However, other symptoms such as hypertension, tachycardia, syncope, anxiety, and panic attacks are also common. Given the prevalence of these symptoms in the general population, diagnosing PCC or PGL can be particularly challenging for clinicians. Additionally, while rare, some patients may be entirely asymptomatic, with the diagnosis being established incidentally through imaging studies or genetic testing that were prompted by positive family history.[4]

Over recent years, there have been significant advancements in the diagnostic imaging modalities used for both the localized and the metastatic disease stages, with a growing utilization of novel radiotracers (eg, ^{68}Ga-DOTATATE PET/CT, Fig. 1). Furthermore, heightened awareness of germline mutations and genetic syndromes associated with PCC and PGL has prompted an increased utilization of germline testing and surveillance protocols. In addition, advancements in surgical techniques, prompted by the shift from open to minimally invasive approaches (laparoscopic or robotic-assisted, Figs. 2 and 3), have reduced surgery-related morbidity. In this review, we aim to highlight the recent advancements in the field concentrating on biochemical testing, imaging modalities, genetic consoling, surgical approaches, advances in the treatment of metastatic disease, and future perspectives.

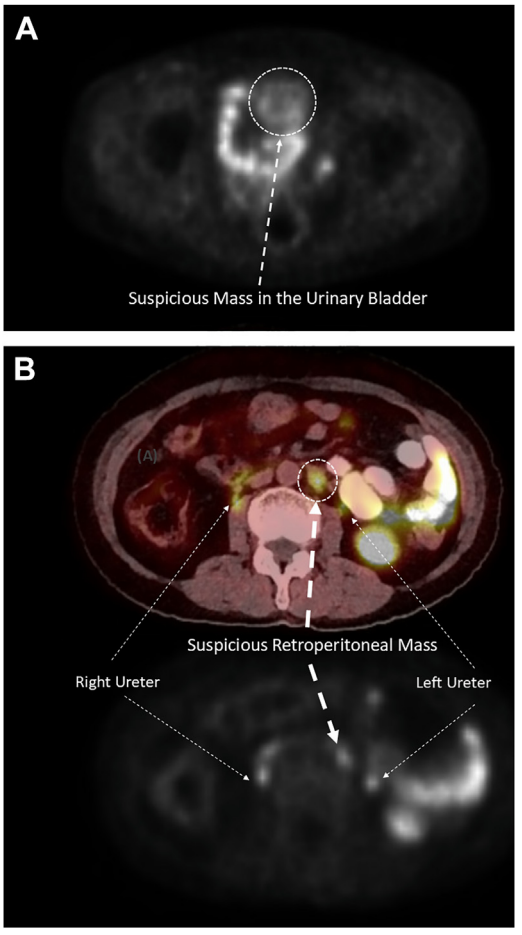

Fig. 1. (*A*) ^{68}Ga-DOTATATE PET/CT images demonstrating the PET images of a suspicious avid uptake in the bladder (marked by a *dashed, thick dashed arrow* and *dashed circle*) of a 75 years asymptomatic female patient with negative biochemical workup who presented with recurrent episodes of hematuria and on transurethral bladder tumor resection, pathology revealed paraganglioma. (*B*) ^{68}Ga-DOTATATE PET/CT images demonstrating the PET image (on the bottom) and the fusion image (in the middle) of a suspicious avid uptake in the para-aortic region in the retroperitoneum (marked by a *thick dashedarrow*).

BIOCHEMICAL TESTING

Biochemical tests are essential for detecting catecholamine secretion by PCC/PGL and remain the cornerstone for diagnosis and monitoring treatment response.[5] Despite advancements in imaging and genetic testing, these biochemical tests continue to be crucial for accurate diagnosis. The indications for biochemical screening based on the natural history of PGL tumors include (1) clinical presentation with catecholamine excess symptoms and signs; (2) imaging detection of incidentalomas or suspicious extra-adrenal lesions[6]; and (3) screening carriers of susceptible germline mutations: For these individuals, plasma or urinary tests are recommended in childhood, with plasma-free metanephrine and normetanephrine preferred for adults. If initial results are negative, repeat

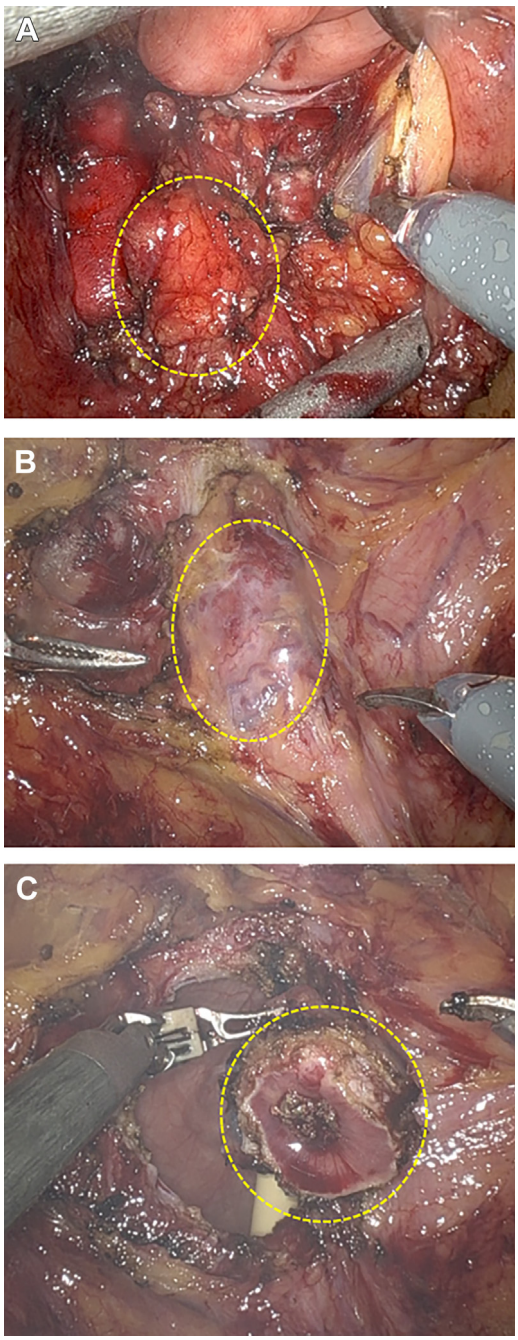

Fig. 2. Intraoperative images of robotic-assisted partial cystectomy with retroperitoneal dissection of a mass suspicious for paraganglioma as demonstrated in Fig. 1. (*A*) A view of the retroperitoneal mass suspicious for paraganglioma, the bowel is lifted and dissected away to expose the retroperitoneal area (the *dashed circle* represents the tissue suspicious for paraganglioma). (*B*) A view of dissected Retzius space, the bladder is visible, note the hypervascular mass that is found extending from the bladder dome to the anterior wall (within the *dashed circle*). (*C*) A view after partial cystectomy was performed. The tumor is held by the Maryland bipolar forceps after it was resected (within the *dashed circle*), the inner part that was facing the bladder demonstrates a central ulcer and adjacent normal appearing bladder mucosa. In the background normally appearing bladder with the Foley catheter in place. On histological examination, a retroperitoneal mass with multifocal paragangliomas arising from the organ of Zuckerkandl, with 9 adjacent lymph nodes negative for tumor. The bladder dome specimen demonstrated a 1.5 cm paraganglioma invading into the muscularis propria, with negative resection margins.

biochemical testing every 2 years during childhood and annually in adults is recommended.[7] For routine testing, plasma-free metanephrines have higher specificity and sensitivity compared to urinary metanephrines.

Chromaffin cell tumors secrete catecholamines directly into the bloodstream, a process primarily regulated by calcium ions (Ca^{2+}).[5] The secretion of catecholamines (epinephrine, norepinephrine, and dopamine) varies across tumors, as metastatic PGLs predominantly produce norepinephrine while other PGLs may also secrete epinephrine. These differences can affect clinical presentation but when alone, are not diagnostic of metastatic PGLs.[8] Catecholamine metabolism is continuous. As a result, 24 hour urine collection tests are less accurate.[9] The preferred method for measurement is liquid chromatography-tandem mass spectrometry (LC-MS/MS), which offers 100% sensitivity. In contrast, enzyme-linked immunosorbent assay is less reliable, with only 74% sensitivity.[10] Many studies on biochemical tests are limited due to design flaws, including small sample sizes, which may affect their validity. Older tests like urinary vanillylmandelic acid (VMA) have shown limited sensitivity and have been replaced by more accurate methods.[5,11]

Blood testing, including plasma-free normetanephrine, metanephrine, and 3-methoxytyramine, is generally superior to urinary metabolites. A more than 2 fold increase above the upper cutoff for plasma measurements is suggestive of a PCC/PGL, provided that accurate measurement methods such as LC-MS/MS and proper blood sampling techniques (ie, 20 minutes in a supine position) are conducted.[9,12,13] The interpretation of these tests should take into account the magnitude and patterns of the results, the pretest probability of having PCC/PGL, the patient's clinical symptoms and signs, and defined reference intervals.[5,14] Current North American Neuroendocrine Tumor Society 2020 guidelines recommend measuring either plasma-free or urine-fractionated metanephrines,

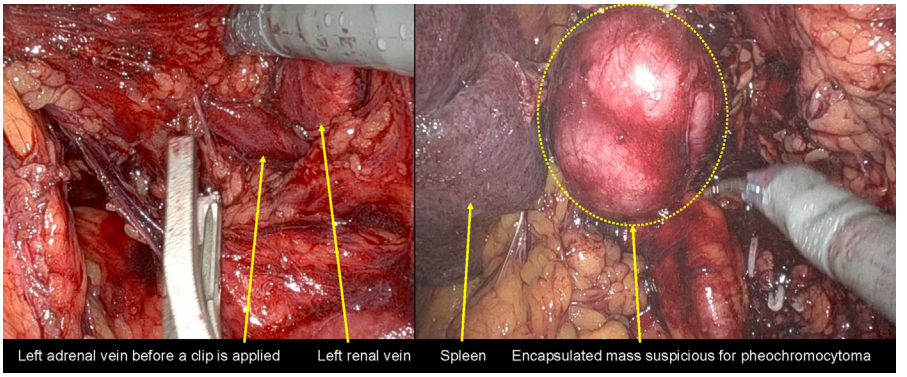

Fig. 3. Intraoperative images of a robotic-assisted transperitoneal left adrenalectomy for a suspicious mass, as shown in Fig. 4. The left image shows the renal hilum and the left adrenal vein prior to clipping. The right image displays an encapsulated, oval mass suspicious of pheochromocytoma (within the *dashed circle*) after it has been dissected from surrounding structures and tissues.

or both as primary biochemical diagnostic tests with a preference toward measuring the fractionated or free metanephrines over the parent catecholamine. Blood sampling should be done in the supine position after 20 minutes of rest. Similarly, The Working Group on Endocrine Hypertension of the European Society of Hypertension recommends for first-line screening the measurement of plasma- or urinary-free normetanephrine and metanephrine, and the use of LC-MS/MS as the preferred measurement method.[9] Fractionated urinary metanephrines are superior to urinary total metanephrines, urinary catecholamines, and urinary VMA, achieving 90% to 100% sensitivity. Plasma-free metanephrines generally perform better than urinary-free or fractionated metanephrines, with Eisenhofer and colleagues[15] reporting 97.9% sensitivity in plasma tests compared to 92.1% in fractionated urinary metanephrines.

Another biomarker in use is chromogranin A (a neuroendocrine tumor biomarker). Chromogranin A is indicated in certain cases of succinate dehydrogenase (SDHx) germline mutation carriers. In combination with imaging studies, chromogranin A can be a valuable biomarker in patients with cluster 1 PGLs and silent PGLs located in the head and neck or thoracoabdominal regions.[7,14,16–18] In cases in which a dopamine-secreting tumor is suspected, fasting plasma-free 3-methoxytyramine should be measured alongside plasma metanephrines.[19]

In unclear presentations, the clonidine suppression test can be performed to differentiate between PCC/PGL and other conditions that cause physiologic elevation of catecholamines (eg, stress, hypertension, and certain medications); it is particularly useful in patients with borderline-increased normetanephrine levels.[20] This test should not be used in cases of exclusive elevation of adrenaline and metanephrine, or in patients taking norepinephrine uptake blockers, or similar medications (eg, beta-blockers, tricyclic antidepressants, and diuretics).[20–22] A new cutoff for plasma normetanephrine measured 180 minutes after clonidine administration, set at 80% of the age-related upper limit of normal, has shown a sensitivity of 94% and specificity of 97%.[23]

False positives in biochemical testing for plasma-free or fractionated metanephrines occur in 20% to 25% of cases. Adhering to strict blood sampling protocols can reduce the need for additional tests.[14,24] Conditions like obstructive sleep apnea and various medications (eg, tricyclic antidepressants, phenoxybenzamine, serotonin-norepinephrine reuptake inhibitors like venlafaxine and duloxetine, selective α1-adrenoceptor blockers like doxazosin, atypical antipsychotics like quetiapine, clozapine, risperidone, and zolpidem, recreational drugs like cocaine and amphetamines, attention-deficit/hyperactivity disorder (ADHD) treatments like methylphenidate, anti-obesity drugs like phentermine, and levodopa [L-DOPA]) increase nocturnal catecholamine release and may cause false positive results. Additionally, withdrawal from sedatives such as benzodiazepines, opioids, clonidine, and alcohol can elevate sympathetic activity, leading to false positive results.[14] Before sampling metanephrines, patients should discontinue all medications that could influence urinary or plasma metanephrine levels for at least 1 month and avoid caffeine-containing beverages within the last 24 hours, particularly if previous tests have shown mild elevations.[9]

DIAGNOSIS AND IMAGING STUDIES

Imaging studies are used to confirm the localization of patients with biochemically positive disease. They can be used both for staging

purposes, discriminating between multifocal, metastatic, or localized disease, and when planning the surgical approach. Their use can be extended to the surveillance period for monitoring treatment response. After biochemical tests confirm the suspicion of PCC, an anatomic imaging study is recommended. For this purpose, a computed tomography (CT) scan with intravenous contrast or MRI scan (not requiring the use of gadolinium-based contrast) are used. The majority of PCC/PGL are found in the abdomen. However, in a subset of patients, including those with SDHx germline mutation carriers, head and neck or mediastinal PGLs are commonly found, hence, abdominal imaging should be supplemented with head and neck or chest imaging to confirm disease localization. In cases when multifocal/metastatic PCC/PGL is suspected or in cases with negative anatomic study and positive biochemical testing, a functional imaging scan using nuclear tracers is recommended.

Anatomic Imaging Studies

CT/computed tomography

CT scan with intravenous contrast provides both anatomic information for tumor localization and the ability to differentiate between adrenal adenoma and other lesions. In the noncontrast phase, an adrenal incidentaloma that measures 10 Hounsfield units (HU) or greater is suspicious for adrenal adenoma with a sensitivity of 47.6% and specificity of 93.3%. Lesions that measure greater than 10 HU require a further washout study using an intravenous administration of contrast material.[25] PCC/PGL tend to have a faster uptake of contrast material and slower washout of the contrast material compared to adrenal adenomas. Hence, in the washout phase, the measurement of the absolute percentage washout of greater than 60% or relative percentage washout of greater than 40% is consistent with adenoma.[26] However, some overlap between adenomas and PCC/PGL may exist—most PCC have low intracellular lipid content, and up to 30% of adenomas can exhibit lipid-poor features. In a meta-analysis of 114 patients with PCC, the sensitivity and specificity of a washout study for differentiating PCC from adrenal adenoma were 97% (93%–99%) and 67% (44%–84%), respectively.[27] Hence, following a washout study, an overlap of 35% remain between PCC and adenoma, this may result in a potential misclassification of PCC as an adrenal adenoma.[28] Therefore, functional imaging using radiotracers are beneficial for patients with positive biochemical testing that require proper disease localization. It is particularly important in cases when there is a suspicion of extra-adrenal disease, metastatic disease, or disease recurrence.

MRI/magnetic resonance imaging

MRI scans provide similar anatomic details as CT scans for PCC and PGL and do not require the use of gadolinium-based contrast material. On MRI, both PCC and PGL demonstrate a hypointense signal on T1-weighted images and a hyperintense signal on T2-weighted images. Historically, two imaging signs were described for adrenal PCC. The first is the "light bulb" appearance that resulted from a significant hyperintense signal from the tumor on T2-weighted images (Fig. 4A-B), and the second is the "salt-and-pepper" appearance that represents the presence of intertwined hypointense and hyperintense signals indicating flow voids from the tumor's vascularity with areas of intratumoral hemorrhage (Fig. 4C). While suggestive, neither of these signs was found to be sensitive or specific for diagnosing PCC/PGL—indeed, up to 35% of cases can be misclassified when using these former "pathognomonic" MRI signs.[29] The commonly used method for MRI in the diagnosis of PCC/PGL is the recognition of the chemical shift ratio between the adrenal gland and the spleen, where the lack of signal dropout on out-of-phase sequences signifies a lipid-poor lesion.[30] However, and similarly to what was described for CT scans with a washout phase, an overlap between adrenal adenomas and PCC exists also for MRI scans using a chemical shift ratio measurement.[31,32] Consequently, differentiating PCC from other adrenal lipid-poor lesions must be paired with results from the metabolic workup and can be supplemented by functional imaging studies.

Functional Imaging Studies

^{131}I/^{123}I-MIBG scintigraphy

131 iodine/ 123 iodine - metaiodobenzylguanidine (^{131}I/^{123}I-MIBG) scintigraphy uses a radiolabeled guanethidine analog that is structurally similar to norepinephrine and binds to norepinephrine receptors and internalized, hence allowing the visualization of neuroendocrine tissue. A meta-analysis found that ^{123}I-MIBG had sensitivity and specificity of 96% and 100% for lesions in the adrenal gland, and 98% and 79% for lesions located outside the adrenal gland, respectively.[33] However, the sensitivity of the scan in patients with SDHx germline mutation carriers is low. Moreover, pharmacologic interference by other agents may block MIBG uptake, leading to a false negative result. The need to perform 24 hour delayed imaging eventually led to its fallout of favor in light of the novel radiotracers used in PET/CT imaging.

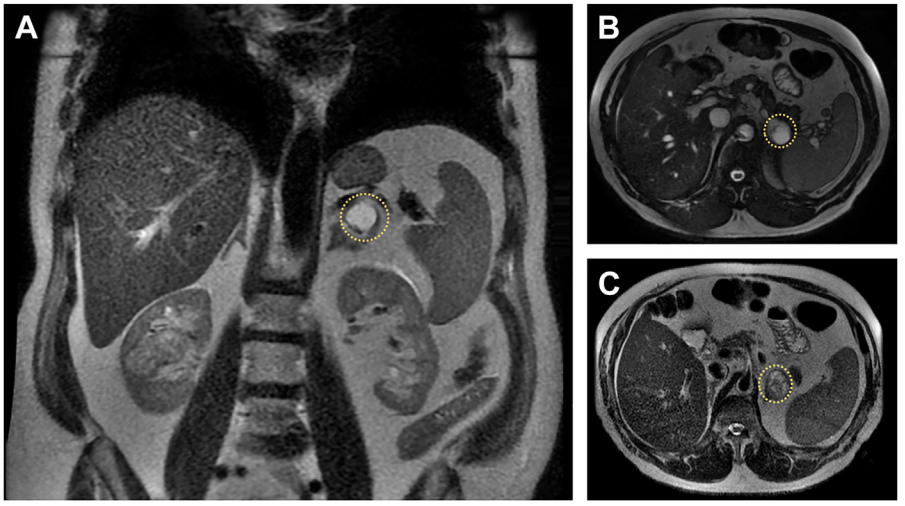

Fig. 4. MRI T2-weighted images of a 76 year old male patient that presented with hypertension and a suspicious lesion on the left adrenal gland. Biochemical tests were positive. (*A*) Coronal image and (*B*) axial image showing an oval, hyperintense lesion (within the *dashed circle*) in the T2-weighted image in the left adrenal region ("light bulb sign"), which is suspicious for pheochromocytoma (note the normal adrenal parenchyma adjacent to the encapsulated mass). (*C*) Axial image depicting the left adrenal mass with areas of hypointensity intertwined with hyperintensity, characteristic of the "salt and pepper" sign, indicative of pheochromocytoma.

^{18}F-DOPA PET/CT

^{18}F-DOPA PET/CT is a radiolabeled amino acid of DOPA, a precursor of dopamine and other catecholamines. DOPA is internalized by the large neutral amino acid transporter to be later converted to dopamine, thus allowing the visualization of neuroendocrine tumors. Changhwan and colleagues performed a prospective comparative study between ^{18}F-DOPA PET/CT and ^{123}I-MIBG scintigraphy in the diagnosis of primary PCC and PGL and found that ^{18}F-DOPA PET/CT was not inferior to ^{123}I-MIBG scintigraphy with sensitivity of 95.7% versus 91.3% and specificity of 88.9% versus 88.9%, respectively. Yet, ^{18}F-DOPA PET/CT had higher sensitivity for detecting metastatic and recurrent disease (86.2% vs 65.5%, respectively, $P = .031$) and had a superior interobserver agreement (k = 0.94 vs 0.85, respectively) than ^{123}I-MIBG.[34] Janssen and colleagues[35] evaluated the utility of ^{18}F-DOPA PET/CT compared to ^{68}Ga-DOTATATE PET/CT for the detection of PCC/PGL in patients with SDH-B subunit mutation and found that ^{18}F-DOPA PET/CT is inferior to ^{68}Ga-DOTATATE PET/CT with respect to lesion-based detection rate (61.4% vs 98.6%, respectively, $P < .01$). The drawback of ^{18}F-DOPA PET/CT remains its low availability in most countries, limiting its wide use.[36]

^{18}F-FDG PET/CT

^{18}F-FDG PET/CT uses a labeled glucose molecule. Glucose is freely up taken by cells physiologically and areas with higher metabolic activity can be detected (eg, cancer, inflammatory, or infectious processes). ^{18}F-FDG PET/CT has been used for staging purposes of PCC and PGL; while not being a specific marker of catecholamine synthesis, most patients with PCC/PGL demonstrate good avidity to ^{18}F-FDG. However, ^{18}F-FDG PET/CT has low sensitivity for detecting lesions in patients with multiple endocrine neoplasia 2 (MEN-2) syndrome. Timmers and colleagues[37] demonstrated a sensitivity of 40% among 10 patients with MEN-2 syndrome, while carriers of SDHB/D and von hippel–lindau disease (VHL) mutations had a sensitivity of 80% and 100%, respectively. Nockel and colleagues[38] evaluated the impact of ^{18}F-FDG PET/CT use on surgical management among 100 patients. The authors demonstrated that ^{18}F-FDG PET/CT detected 15 additional lesions over conventional imaging modalities; of the 15 lesions, 7 were detected for the initial operation, and 8 for the reoperations; lesions were detected in the retroperitoneum, liver, and bone. Chang and colleagues[39] compared ^{68}Ga-DOTATATE PET/CT to ^{18}F-FDG PET/CT in 23 patients and found statistically comparable detection rates between the imaging modalities (96.2% vs 91.4%, respectively), although ^{68}Ga-DOTATATE PET/CT demonstrated greater lesion to background contrast than ^{18}F-FDG PET/CT. Additionally, PCC/PGL with aggressive behavior may demonstrate a rapid shift in imaging patterns due to dedifferentiation of the

tumor and increased metabolic activity, which can be better visualized by ^{18}F-FDG PET/CT than by somatostatin-labeled radiotracers (eg, ^{68}Ga-DOTATATE). Furthermore, ^{18}F-FDG PET/CT has the advantage of being more prevalently utilized and available worldwide, hence, it remains a valuable tool in the management of non-MEN-2 PCC/PGL. Of note, ^{18}F-FDG PET/CT avidity should be weighed against other potential differential diagnoses that include other solid tumor metastases, hematological diseases like lymphoma, and adrenocortical carcinoma.[36]

^{68}Ga-DOTATATE and ^{64}Cu-DOTATATE PET/CT

DOTATATE is a somatostatin analog conjugated to dodecane tetra-acetic acid) that can be combined with ^{68}Ga, ^{177}Lu, or ^{64}Cu and used in the imaging of PCC/PGL (see **Fig. 1**), as these tumors are known to express elevated levels of somatostatin receptors (SSTRs).[36] Copper-64 has a longer half-life of 12.7 hours versus 68 minutes for ^{68}Ga, which allows easier handling and the performance of delayed images and dosimetry with ^{64}Cu; however, it comes with the expense of higher radiation burden that should be considered when comparing to ^{68}Ga.[40] As mentioned previously, ^{68}Ga-DOTATATE PET/CT was found to be superior to other imaging modalities for carriers of SDHx germline mutation carriers.[35] Patel and colleagues[41] demonstrated that in patients with PGL with SDH-A mutation, ^{68}Ga-DOTATATE PET/CT was superior in lesion detection over ^{18}F-FDG PET/CT, ^{18}F-DOPA PET/CT, and CT/MRI with detection rates of 88.6%, 82.9%, 39.8%, and 58.9%, respectively. Matti and colleagues found that ^{68}Ga-DOTATATE PET/CT had a sensitivity of 88% for adrenal PCC and 100% for abdominal PGLs, recommending its use in the primary assessment of all PGLs.[42] Combined, ^{68}Ga-DOTATATE and ^{64}Cu-DOTATATE PET/CT have become the cornerstone of staging and follow-up in patients with metastatic PGL, particularly in SDHx germline mutation carriers.[36]

GENETIC COUNSELING

Historically, PCC/PGL were considered sporadic; however, emerging evidence indicates that up to 40% of patients harbor germline mutations that increase the risk of developing PCC/PGL. In particular, individuals younger than 45 years or those presenting with multifocal, bilateral, or recurrent lesions exhibit a higher likelihood of possessing these mutations. Consequently, genetic counseling with a medical geneticist is strongly recommended for these patients, enabling comprehensive risk assessment and guiding management strategies for both the individuals at risk and their family members.[43]

Several hereditary syndromes have been found to contribute to the development of PCC/PGL. Approximately 70% of PCC/PGL can be categorized into 3 clusters based on genetic mutations, exhibiting distinct clinical behaviors and biochemical expressions. Tumors in the pseudohypoxia Krebs cycle/VHL/endothelial PAS domain protein 1 (EPAS1) cluster 1 typically have a noradrenergic phenotype, while those in the kinase-signaling cluster 2 usually have adrenergic phenotypes. Cluster 3 is related to Wnt signaling and has been incompletely elucidated, yet, evidence suggests that it is may be associated with a more aggressive tumor behavior.[16]

Von Hippel–Lindau syndrome is a rare hereditary autosomal dominant disorder that arises from a mutation in the VHL gene, a tumor suppressor gene located on chromosome 3. VHL is responsible for the ubiquitin-related degradation of hypoxia-inducible factor (HIF). VHL mutation results in overactivity of HIF leading to the development of hypervascular tumors, such as PCC.[44,45] In 19% of patients with VHL, PCC is part of the clinical manifestations, and commonly appears before the third decade of life.[46,47] Patients with type 2 VHL have an overall PCC prevalence of 60%, and those with type 2C have the highest prevalence of PCC at 84%. Most patients with VHL develop bilateral adrenal involvement (60%), both in synchronous and in metachronous manner. According to the current National Comprehensive Cancer Network (NCCN) guidelines, patients with VHL are recommended to start blood pressure monitoring from the age of 2 years and have an annual measurement of plasma-free metanephrines (preferred) or 24 hour urine collected for fractionated metanephrines starting at the age of 5 years. Cross-sectional imaging (MRI or CT) is recommended from the age of 15 years and should be performed in 2 to 3 year intervals.[43]

MEN-2 is a rare autosomal dominant hereditary syndrome that is caused due to a mutation in the rearranged during transfection (RET) proto-oncogene.[48] Medullary thyroid carcinoma remains the hallmark of the syndrome, and PCC develops in 50% of MEN-2 mutation carriers. Approximately 50% of patients with MEN-2 develop bilateral adrenal involvement by the third decade of life.[49] Current NCCN guidelines recommend surveillance starting from the age of 11 years for the American Thyroid Association high-risk and highest risk groups, and starting at the age of 16 years for the American Thyroid Association moderate-risk group. Like VHL, NCCN guidelines recommend surveillance with annual plasma-free

metanephrines or 24 hour urine collection for fractionated metanephrines starting at age 5 years and cross-sectional imaging (MRI or CT) performed at a 2 to 3 year interval starting at the age of 15 years.[43]

SDHx germline mutation carriers have a mutation in the gene that encodes the 4 subunits of the mitochondrial succinate dehydrogenase enzyme. Succinate dehydrogenase is a mitochondrial citric acid cycle enzyme and is part of cellular respiration and energy production. Mutations in succinate dehydrogenase give rise to a pseudohypoxic state while having a normoxic condition. Different pathogenic variants have been described for SDHx mutation carriers, including subtypes A–D; of these SDH-B and SDH-D are more commonly identified among patients with PCC and PGL. SDH-B have an estimated PCC/PGL penetrance rate of 20% to 30% by the seventh decade of life, and 70% to 80% of the tumors are of extra-adrenal sympathetic origin. Approximately 20% to 30% develop parasympathetic head and neck, and anterior mediastinum tumors. Carriers of SDH-D mutation develop PCC/PGL in 25% of the cases and have an overall lower malignancy risk than SDH-B mutation carriers.[7] Surveillance should be started at the age of 6 to 10 years for patients with SDH-B mutations and at the age of 10 to 15 years for patients with all other forms. Blood pressure monitoring is recommended at all medical visits. Annual measurement of plasma-free metanephrines or 24 hour urine for fractionated metanephrines is also recommended. Cross-sectional imaging using whole-body MRI from the skull base to the pelvis should be performed with intervals of 2 to 3 years. If whole-body MRI is not available, a combination of abdominal MRI, skull base and neck MRI, and chest CT can be considered. Since SDHx genes have variability in their tumor penetrance and risk for malignancy, consideration can be given to modified screening intervals, especially for less-penetrant genes such as SDH-A mutation. Asymptomatic carriers without a prior history of catecholamine elevation can have the annual follow-up and testing omitted and replaced with cross-sectional imaging performed at intervals of 2 to 3 years.[43]

SURGICAL MANAGEMENT

Surgical removal is the primary treatment of PCC of any size.[50] Over the years, surgical techniques have evolved significantly, transitioning from open surgery to minimally invasive procedures. These include both traditional laparoscopic and robotic-assisted approaches that utilizes either the multiport or single-port robotic systems; both approaches may be performed via either the transperitoneal or the retroperitoneal route.[51–53] The laparoscopic approach is the gold standard for adrenalectomy, as it is superior to the open approach in terms of decreased hospital stay, intraoperative blood loss, and overall complication rates.[52,54,55] Despite the broad adoption of minimally invasive techniques, mastering the open technique is essential in specialized centers. The open approach is more likely to be used in cases of large PCC tumors (>8–10 cm) and must be utilized when suspicion exists for local invasion, adrenocortical cancer, extension into major veins, and in cases of indicated conversion in complicated minimal invasive surgery.[56] There are noteworthy differences between minimally invasive transperitoneal and retroperitoneal approaches. For instance, the retroperitoneal approach, obviates the need for intestinal mobilization and intraperitoneal insufflation, thereby, reducing postoperative pain and the incidence of postoperative ileus. Additionally, the procedure offers a potentially shorter operative time. Conversely, the retroperitoneal approach is challenging to learn due to the relative lack of surgical landmarks, offers limited surgical space, and could be challenging for large tumors.[57] Although retrospective analyses have demonstrated similar operative time and complication rates to laparoscopic adrenalectomy, robotic-assisted approach (see **Figs. 2** and **3**) is associated with decreased blood loss and hospital stay.[58] Single-port robotic adrenalectomy is a recent addition to our surgical tools. While there are limited analyses to date, the initial results for single-port robotic surgery are encouraging.[53] The choice of surgery should consider both patient-related and surgeon-related factors; performing these surgeries in specialized centers with experience in adrenal surgeries is recommended. Importantly, regardless of the approach chosen, when handling adrenal pheochromocytoma, the surgeon should avoid handling or manipulating the tumor till the adrenal vein is controlled and clipped. Commonly, the left adrenal vein drains into the left renal vein, and on the right side directly to the posterolateral aspect of the inferior vena cava. This is done in order to ensure minimal release of catecholamines to the circulation while handling the adrenal gland and the tumor (see **Fig. 3**).

While there are heterogeneous practice patterns with regard to preoperative management of patients with PCC, one common approach includes preoperative alpha blockade starting at least 10 days before surgery to decrease intraoperative hemodynamic instability during tumor manipulation.[59] This is followed by the addition of beta

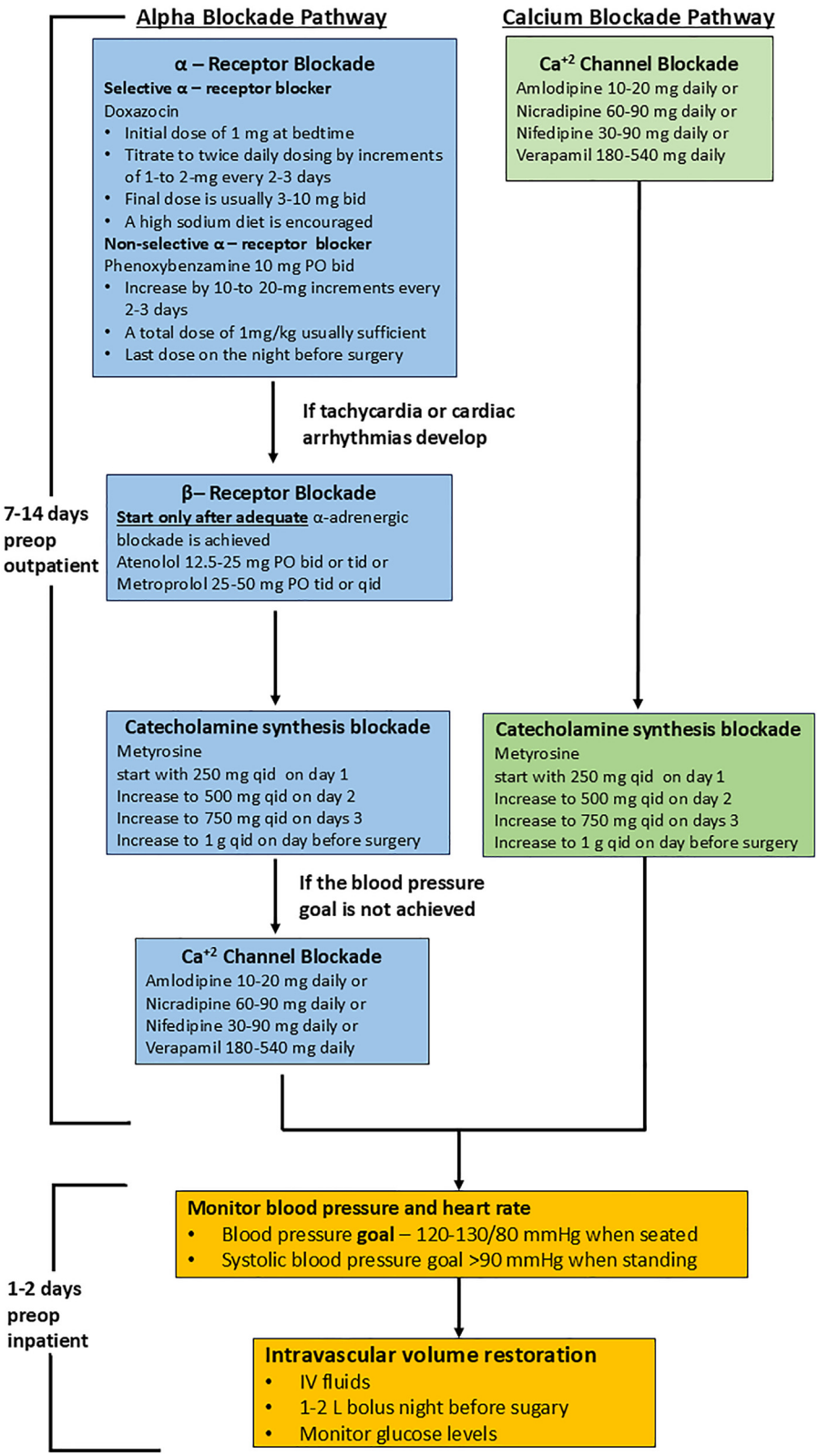

Fig. 5. Flowchart demonstrating the different perioperative approaches using either alpha-adrenergic blockade or calcium channel blockade to achieve adequate blood pressure control in metabolically active tumors. (*Adapted from* Waingankar et al.[27])

blockade if necessary due to reflex tachycardia. Other options include catecholamine synthesis blockade and calcium channel blockade (Fig. 5). All patients should be adequately hydrated preoperatively, and intraoperatively glucose levels and ensuing hypoglycemia should be anticipated and corrected.[27]

Subtotal cortical sparing adrenalectomy, which involves the preservation of about 15% to 30% of cortical tissue, should be considered in patients with or at risk for bilateral disease to avoid lifelong steroid replacement therapy and related complications.[50] Although this approach has a higher risk of recurrence, it does not affect overall survival.[51,60]

METASTATIC PHEOCHROMOCYTOMA/ PARAGANGLIOMA

Treatment of metastatic PCC and PGL is often complex and requires a multimodal approach with limited data on the efficacy of combined treatment options.[61]

The 2024 NCCN guidelines advocate for similar treatment options for both locally unresectable disease and metastatic disease, including enrollment to a clinical trial, treatment with radioligand labeled high specific activity (HSA) iobenguane ^{131}I-MIBG (requires prior positive MIBG scan), sunitinib 37.5 mg once daily (a TKI—tyrosine kinase inhibitor), systemic chemotherapy, peptide receptor radionuclide therapy (PRRT) with ^{177}Lu-DOTATATE (if SSTR-positive), or somatostatin analogs (octreotide long-acting release [LAR] or lanreotide, if SSTR-positive). While covering all the possible treatments available extends beyond the focus of this review, several novel treatment modalities should be mentioned.[43]

Iobenguane ^{131}I-MIBG currently is the only Food and Drug Administration-approved therapy for metastatic PGL, based on the IB12B open-label, single-arm trial (NCT00874614) for patients aged 12 years or older with positive MIBG scan; among 68 patients, 25% demonstrated a 50% or greater reduction of all hypertensive medication and the overall tumor response was 22% (95% confidence interval [CI] 14–33); 53% achieved a response duration of at least 6 months. However, 6.8% of the patients developed myelodysplastic syndrome or acute leukemia.[62]

Two trials sought to investigate the use of ^{177}Lu-DOTATATE-based PRRT. Jaiswal and colleagues[63] evaluated 15 patients with unresectable or metastatic PGL and Krenning score above 2 with low I-MIBG uptake. SSTR response was based on ^{68}Ga-DOTATATE PET/CT. The median duration of follow-up was 27 months and overall survival was 100%. Seven patients (47%) had stable disease and 3 patients (20%) developed disease progression. Common side effects were nausea (20%) and weight loss (13%). Two patients had hematological disturbances (anemia and/or thrombocytopenia). Vyakaranam and colleagues[64] evaluated ^{177}Lu-DOTATATE with PRRT in 22 patients with PCC and PGL (2 were localized and 20 metastatic). Two patients had a partial response and 20 had stable disease. The median overall survival was 49.6 months, and the progression-free survival was 21.6 months. No hematological or nephrotoxicity grade 3 or greater adverse events were documented. Although promising, the current evidence to support the use of ^{177}Lu-DOTATATE in unresectable and metastatic PGL remains limited.

The use of TKI was explored in 2 trials. In a phase 2 trial, the investigators of FIRSTMAPPP randomized 78 patients with metastatic PCC and PGL (1:1) to receive either placebo or 37.5 mg of sunitinib. Twenty-five patients (32%) were SDHx germline mutation carriers. The overall 12-month progression-free survival was 36% (90% CI 23–50) versus 19% (90% CI 11–31) in the placebo arm. Patients with SDHx germline mutation carriers had demonstrated a higher response rate to sunitinib than the overall population. While no overall survival benefit was demonstrated for sunitinib, sunitinib did demonstrate a high level of antitumor activity in patients with progressive metastatic PGL.[65] In another recent phase 2 single-arm trial (the Natalie trial), the investigators used cabozantinib (TKI) in 17 patients with unresectable and progressive metastatic PGL, and a median follow-up time of 25 months; the overall response rate was 25% (95% CI 7.3–52.4).[66] Notably, while both TKIs have shown limited efficacy in metastatic PCC/PGL, their oral administration and broad availability render them more accessible, similar to other systemic treatments, such as chemotherapy. This is in contrast to advanced imaging techniques and radionucleotide-labeled particles, which are not universally available, highlighting the critical need for ongoing research and integration of these therapies for the treatment of metastatic and progressive PCC/PGL.

Lastly, limited evidence indicates that surgical management may be also beneficial in the metastatic setting. In a cohort of 25 patients with a median 9 year follow-up, Verissimo and colleagues[67] suggested that surgical intervention should remain an important centerpiece of the treatment of metastatic PGL. The authors reported a complete response in 87% of patients following surgical resection of the primary tumor, and in 87.5% of patients through tumor debulking or metastasectomy.

DISCUSSION AND FUTURE PERSPECTIVES

PCC and PGL present significant challenges in diagnosis and management due to their rarity, variable clinical presentation, and the potential for malignancy and metastatic spread. The advancements in biochemical testing, imaging modalities, genetic counseling, and surgical management have substantially improved patient outcomes, yet the complexity of these tumors continues to require a multidisciplinary approach. The evolution of biochemical testing has provided more accurate and reliable methods for diagnosing PCC/PGL. Plasma-free metanephrines, measured by LC-MS/MS appear to provide good sensitivity and specificity. However, clinicians should be vigilant in detecting physiologic and pharmacologic factors that can cause false elevations, adhering to strict pretesting protocols, and using the clonidine suppression test in borderline cases. While CT and MRI scans provide excellent anatomic information, novel functional imaging, such as ^{68}Ga-DOTATATE PET/CT, have improved the detection of metastatic and multifocal disease, particularly in patients with germline mutations like SDHx, shifting to their use in metastatic and recurring PGL. However, access to these advanced imaging techniques remains limited in many regions, posing a barrier to optimal patient care. More widely available tracers, such as ^{18}F-FDG PET/CT, provide a good modality for staging PCC/PGLs in cases not associated with MEN-2 syndrome. In addition, the identification of hereditary syndromes associated with PCC/PGL and their higher than previously thought prevalence highlight the importance of genetic counseling in the management of these patients. Syndromes such as VHL, MEN-2, and SDHx mutations require tailored surveillance strategies for early tumor detection and the consequent reduction in morbidity. Furthermore, urologists should be familiar with non-genito-urinary (GU) manifestations of these hereditary syndromes and their risk of bilateral adrenal disease.

Surgical management remains the cornerstone of treatment of PCC/PGL, and minimally invasive approaches offer reduced morbidity and faster recovery times. However, open surgery retains a critical role in cases of larger tumors, or complex anatomic locations. Robotic-assisted surgery, including the single-port approach, represents a promising advancement, though further studies are needed to establish its long-term outcomes and broader applicability.

The management of metastatic PCC/PGL represents one of the most pressing challenges in the field. Current treatment options, including systemic therapies such as TKIs (sunitinib and cabozantinib), radioligand therapy with ^{131}I-MIBG, and PRRT with ^{177}Lu-DOTATATE, have shown promise but are limited by accessibility and variable efficacy. The development of targeted therapies, potentially informed by the genetic and molecular profile of individual tumors, could revolutionize the treatment landscape. Exploration of novel biomarkers and radiotracers holds the potential to enhance early detection, and to monitor disease progression and treatment response more accurately, ultimately improving survival rates and quality of life.

In conclusion, while significant progress has been made in understanding and managing PCC/PGL, several challenges remain, particularly in the treatment of metastatic disease. Minimally invasive approaches allow the reduction of surgical morbidity and provide better cosmesis, particularly in young patients. However, multidisciplinary collaboration among endocrinologists, radiologists, medical geneticist, surgeons, and oncologists remains critical for improving disease outcomes.

CLINICS CARE POINTS

- Clinicians should maintain a high index of suspicion of recognizing symptoms suggestive for pheochromocytoma and paraganglioma (headaches, palpitations, sweating, or unexplained hypertension). Given that hereditary germline mutations are identified in up to 40% of patients with PCC/PGL, it is imperative that appropriate genetic counseling and testing should be offered to individuals at risk.
- Combine biochemical testing with a tailored imaging approach. Anatomic imaging using either abdominal CT or MRI scan remains the cornerstone diagnostic scan of localizing pheochromocytoma to the adrenal gland. Functional imaging with novel radiotracers, preferably DOTATATE PET/CT should be reserved for patients with inconclusive results, hereditary germline mutations, and for patients with suspicion for disease recurrence.
- Preoperative management of patients with pheochromocytoma requires adequate blood pressure control. It can be achieved with alpha blockers or calcium channel blockers. Additional agents, such as beta blockers, may be used to manage reflex tachycardia, while catecholamine synthesis inhibitors can be employed for further blood pressure control. It is essential that all patients are well-hydrated prior to surgery.
- Minimally invasive approaches, including laparoscopic or robotic-assisted techniques,

should be favored when feasible. Regardless of the chosen approach, to minimize catecholamine release into the circulation when manipulating the tumor, the surgeon should first identify and clip the adrenal vein. For atypical or complex cases, a multidisciplinary approach is strongly recommended.

- Long-term and potentially lifelong follow-up using imaging studies and biochemical testing is crucial even after curative surgery. Surveillance protocols should be tailored for patients who are carriers for known genetic mutations associated with PCC/PGL.

DISCLOSURE

The authors have no conflict of interests or disclosures to declare.

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