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Precision Surgery for Pheochromocytomas and Paragangliomas

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Abstract

Since Felix Fränkel's account of pheochromocytoma in 1886, great discoveries and vast advancements in the diagnosis, genetics, anatomical and functional imaging techniques, and surgical management of pheochromocytoma and paraganglioma (P-PGL) have been made. The improved insight in the pathophysiology of P-PGL and more accurate detection methods enable physicians to tailor the treatment plan to an individual based on the genetic profile and tumor behavior. This review will cover briefly the clinical features, diagnosis, genetic mutations, and imaging modalities that are used to guide current surgical management of these rare and interesting endocrinopathies.

Keywords

pheochromocytoma; paraganglioma; precision surgery; clusters; biochemical phenotypes; genetic testing; anatomic and functional imaging

Introduction

Pheochromocytomas and paragangliomas (P-PGLs) arise from the chromaffin cells of the adrenal medulla and extra-adrenal neural crest tissues from the skull base to the pelvis [1, 2]. These tumors can involve the parasympathetic cervical ganglia and sympathetic ganglia in the thorax, abdomen, and pelvis. P-PGLs are rare and the incidence is approximately 2–8 per million per year. Four to 8% of adrenal incidentalomas have been found to be pheochromocytoma(s) [2]. The clinical and morphological findings of pheochromocytoma were first described in a 18 year old female patient with bilateral adrenal masses in 1886 by a German physician, Felix Fränkel [3]. Dr. Fränkel's patient died suddenly and his description of the account was consistent with hypertensive crisis and myocardial infarction [4]. Dr. Fränkel postulated that the tumor secreted a substance into the veins causing the sequelae that were observed [3]. Bilateral adrenal lesions were found post-mortem. Autopsy and histological analysis were performed by Rudolf Maier and Max Schottelius, respectively. Dr. Schottelius was credited with the first histopathological description of pheochromocytoma [4]. Over ten years following the first case report of pheochromocytoma,

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Conflict of Interest

The authors declare that they have no conflict of interest.

Moore at University College London characterized the physical and biochemical properties of adrenal extract and laid the platform for purification of the active substance [5], which was first successfully performed independently by John Abel in 1899 at Johns Hopkins University [6], and by the Japanese scientist Jokichi Takamine. Takamine purified an extremely potent vasopressor substance and obtained a stable crystalline compound from the adrenal glands of sheep and oxen and named it adrenaline [7]. In 1926, the first successful open resections for pheochromocytoma were performed on two different continents by Dr. Charles Mayo in the United States and Dr. Cesar Roux in Switzerland, and pheochromocytoma was defined and named based on the tumor's affinity for chromium salts [8, 9]. In 1992, Dr. Gagner and colleagues described the first laparoscopic adrenalectomy for pheochromocytoma [10]. More recently, an article in the New England Journal of Medicine from 2007, brings Dr. Fränkel's account of pheochromocytoma full circle by providing molecular evidence that his young patient had multiple endocrine neoplasia type 2 A syndrome (MEN2A) by identifying four of her living relatives with germ-line *RET* mutations consistent with MEN2A [11] and pheochromocytoma being part of the MEN2A phenotype.

Since Fränkel's account of pheochromocytoma in 1886, great discoveries and vast advancements in the diagnosis, genetics, anatomical and functional imaging techniques, and surgical management of P-PGLs have been made. The improved insight into the pathophysiology of P-PGL and more accurate detection methods enable physicians to tailor the treatment plan to an individual based on the genetic profile and tumor behavior. This review will cover briefly the clinical features, diagnosis, genetic mutations, and imaging modalities that are used to guide current surgical management of these rare and interesting endocrinopathies.

Clinical features

Clinical presentations of patients with P-PGLs are typically related to the tumor mass, which can be symptomatic or incidentally identified by the patient, physician, or by imaging studies and/or symptoms associated with excessive catecholamine release. Pheochromocytoma (PHEO) are derived from chromaffin cells of the adrenal medulla that secrete epinephrine, norepinephrine, and their metabolites while paraganglioma (PGL) are extra-adrenal neoplasms associated with the parasympathetic and sympathetic paraganglia along the paravertebral axis that may or may not secrete catecholamines [12]. For example, it is uncommon for cervical PGL associated with the parasympathetic autonomic system to secrete norepinephrine but up to 30% may secrete increased levels of dopamine or its metabolite 3-methoxytyramine (3-MT); the rest may be biochemically silent [13, 14]. P-PGLs which secrete catecholamines may manifest with the classic triad of headache, palpitations, and diaphoresis associated with hypertension. Less common features include abdominal pain, anxiety, heat intolerance, constipation, and pallor. The symptoms and signs may be paroxysmal with up to one-half of patients with P-PGLs having sustained hypertension. Paroxysms can be exacerbated by many actions including, but not limited to, alcohol consumption, strenuous activity, micturition, defecation, labor and delivery, minor surgical procedures, and general anesthesia. Medications that can precipitate a catecholamine crisis include, but are not limited to, dopamine D2 receptor blockers, beta-

adrenergic receptor blockers, opioids, sympathomimetics, anticholinergics, norepinephrine and serotonin reuptake inhibitors, monoamine oxidase inhibitors, corticosteroids, neuromuscular blocking agents, and peptides [adrenocorticotrophic hormone (ACTH) and glucagon] [2, 15–18]. Sequelae of excessive catecholamine secretion can include glucose intolerance, diabetes mellitus, myocardial infarction, heart failure, cerebrovascular accident (CVA), and death. Patients with sympathetic P-PGLs have a 10-fold risk of cardiovascular complications as compared to those without P-PGLs [19]. Eleven percent of patients with P-PGL were noted to have acute catecholamine cardiomyopathy resulting severe left ventricular dysfunction in a series of 140 patients with P-PGL [20]. In addition, patients with P-PGLs can present with other syndromes associated with additional hormones produced by the tumor. Co-secretion of neuropeptides in addition to catecholamines can occur. These elaborated substances may include calcitonin, vasoactive intestinal peptide, neuropeptide Y, ACTH, atrial natriuretic factor, growth hormone releasing factor, and parathyroid hormone-related peptide. Some neuropeptides give rise to specific clinical syndromes such as watery diarrhea with hypokalemia in VIP-secreting tumors and Cushing's syndrome in ACTH-producing tumors [21–23].

Clinical suspicion of a P-PGL increases in patients with hypertension presenting with paroxysmal headaches, tachycardia, palpitations, arrhythmias, anxiety, unintentional weight loss, and or diaphoresis. Suspicion of P-PGLs may also be present with exacerbation of hypertension with the initiation of beta-adrenergic receptor blocker therapy [24]. Early onset hypertension in children and family history of P-PGL or heritable syndromes may offer clues to the diagnosis. New onset hypertension in pregnancy, after pre-eclampsia has been ruled out, should be investigated for possible P-PGL.

Head and neck PGLs (HNPGs) often have an indolent growth velocity with doubling times greater than 10 years [25] and may remain undetected for years. Invasion of cranial nerves or impingement by mass effect can result in hearing loss and/or pulsatile tinnitus (tympanic or jugular foramen tumors), hoarseness and/or dysphagia (vagal body tumors), and/or cranial nerve palsy [26, 27], and much less commonly stroke [28]. Carotid body tumors (CBTs) originating from the carotid body which is a small chemoreceptor located at the posteromedial aspect of the carotid bifurcation are the most common HNPG [29] and usually present as a painless neck mass [28, 29].

The incidence of adrenal incidentaloma detected on imaging is about 8.7% [30]. Approximately 5% of adrenal incidentalomas will be PHEO [31]. Incidentally detected adrenal tumors, or any tumors along the paravertebral axis that enhance with contrast imaging should alert the clinician to rule out PGL before pursuing biopsy or surgery to prevent possible hypertensive complications.

Diagnosis

Diagnosis of P-PGLs begins with a complete history and physical examination and is accomplished through biochemical testing in functioning tumors. Because not all P-PGLs continuously elaborate catecholamines, a single temporal biochemical assay for norepinephrine and epinephrine may miss up to 30% of cases. Catecholamines (dopamine, norepinephrine, and epinephrine) may be synthesized from the essential amino acid

phenylalanine, which is converted to tyrosine or synthesized directly from tyrosine, which is then converted to DOPA with the rate limiting enzyme tyrosine hydroxylase (TH). DOPA is decarboxylated to dopamine and dopamine is enzymatically converted to norepinephrine. Norepinephrine is methylated by phenylethanol-N-methyltransferase (PNMT) resulting in epinephrine. Dopamine, norepinephrine, and epinephrine are metabolized to their respective O-methylated metabolites 3-methoxytyramine (3-MT), normetanephrine, and metanephrine via the enzymatic action of catechol-O-methyltransferase (COMT). Accurate tests focusing on the metabolites of norepinephrine and epinephrine are favored as the metabolites from the parent catecholamine molecules are more consistently released into the serum over-time independent of catecholamine levels [32]. Highly sensitive and specific tests for the initial workup per the 2014 Endocrine Society Practice Guideline [2] include plasma free or 24-hour urinary fractionated metanephrines. Patients with HNPGLs usually do not present with symptoms associated with catecholamine excess since tumors do not produce norepinephrine or epinephrine. However, HNPGLs can secrete dopamine and its metabolite 3-MT, which are often clinically silent.

P-PGL detection was improved in 22% of cases in a National Institutes of Health cohort of 45 patients with succinate dehydrogenase subunit B (*SDHB*) mutation when measurement of serum chromogranin A (CgA) was used in addition to plasma normetanephrine; the authors suggested CgA as a complementary bio-marker to normetanephrine in this subset of *SDHB* mutated P-PGLs to facilitate diagnosis [33]. Together these biochemical tests may accurately reveal the biochemical phenotype of the P-PGLs. Improved sensitivities of the plasma assays are achieved by having the patient fast the evening before morning testing and should be drawn after the patient has rested in the supine position for half an hour [34]. False elevations can be avoided by holding certain drugs such as acetaminophen, alpha-methyl dopa, tricyclic antidepressants, mesalamine, sulfasalazine, phenoxybenzamine, monoamine oxidase inhibitors, sympathomimetics, cocaine, and levodopa, if tolerated by the patient. A three to four-fold increase beyond the upper limit of normal in metanephrine concentrations above age-adjusted reference levels carries a high sensitivity and specificity for the disease and is virtually pathognomonic for P-PGL [24].

Biochemically silent PGLs can pose diagnostic challenges. These include HNPGL, rare biochemically silent PGLs have been documented with *SDHB* mutation [35], other examples include very small (< 1 cm) tumors [36] producing levels of O-methylated metabolites below assay thresholds. Many of these PGLs do not express TH thus, measuring CgA and pursuing anatomic imaging studies can help characterize these tumors [35]. Diagnosis of these tumors may be aided with functional PET/CT imaging including ⁶⁸Ga-tetraazacyclododecane tetraacetic acid octreotate (DOTATATE) PET/CT. Some PGLs can be more easily diagnosed with the addition of ¹⁸F-dihydroxyphenylalanine (DOPA) PET/CT [37, 38].

Genetics

At least one-third of P-PGLs are associated with heritable neoplastic syndromes, which are the highest among all tumors [39]. Germline mutations associated with P-PGLs can be identified in up to 40% of patients with P-PGLs [39]. Of the pediatric patients with P-PGLs,

88% carry germline mutations [40]. All patients diagnosed with P-PGLs should have genetic testing and family members of patients with heritable forms should be offered testing [2, 41]. The results of genetic testing can affect a surveillance plan and surgical management of the affected [42] as well as help determine the genetic status of relatives at risk. Positive benefits of early genotyping in a P-PGL cohort was demonstrated by a French study. A set of 221 patients with P-PGL with *SDHB*, *SDHC*, *SDHD*, or *VHL* germline mutations revealed that patients who knew their genetic mutation within one year of initial P-PGL diagnosis compared to patients knowing their genetic mutation more than a year after initial diagnosis had improved follow-up (more frequent examinations, less patients lost to follow-up), smaller size of subsequent new P-PGLs discovered, lower metastatic spread, and improved 5 year survival rate in the patients who developed metachronous metastases [43]. Germline and somatic mutations in more than 20 genes (*EPAS1*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *VHL*, *EGLN1/2*, *EH*, *MDH2*, *IDH*, *RET*, *NF1*, *H-RAS*, *K-RAS*, *TMEM127*, *MAX*, *ATRX*, *CSDE1*, *MAML3*, *DNMT3A*, *SLC25A11*, *GOT2*, *IDH3B*, *KMT2D*) [44–49] have been identified that lead to the development of P-PGL [50]; many of the germline mutations are readily discovered with the next-generation sequencing method with 98.7% sensitivity [51, 52].

A novel pan-genomic bioinformatic analysis from 2017, of a TCGA (The Cancer Genome Atlas) cohort of 173 patients with P-PGLs have led to distinct molecular clustering containing mutations with similar biology and pathogenesis [48]. The integrative pan-genomic study of P-PGLs with various germline and somatic mutations showed that the gene expression of P-PGLs can be uniquely divided into 3 clusters with unique molecular, clinical, biochemical, and imaging phenotypes [48]. Cluster1 is the pseudohypoxic group containing germline mutations subdivided into a tricyclic acid cycle (TCA) subgroup and *VHL*/*EPAS1* (endothelial PAS domain protein 1) subgroup. The TCA subgroup contains succinate dehydrogenase complex subunit (*SDHx*) mutations (*SDHA*, *SDHB*, *SDHC*, *SDHD*), succinate dehydrogenase complex assembly factor 2 (*SDHAF2*) mutations, and fumarate hydratase (*FH*) mutations leading to the increased concentration of TCA metabolites succinate and fumarate. Accumulation of fumarate and succinate leads to oncogenesis [53–56]. In cells with dysfunctional succinate dehydrogenase the excess succinate accumulated acts as an oncometabolite competitively inhibiting many 2-oxoglutarate-dependent dioxygenases such as prolyl-hydroxylases leading to the inappropriate stabilization of hypoxia-inducible transcription factors (HIFs) HIF 1- α and HIF 2- α resulting in a pseudohypoxic state, inhibition of ten-eleven translocation (TET) enzymes causing increased DNA methylation, and inhibition of Jumonji C-domain-containing proteins (demethylases) leading to increased histone methylation [57]. The *VHL*/*EPAS1* subgroup contains mutated *VHL* and *EPAS1* genes that aberrantly stabilize HIF 1- α and HIF 2- α . These HIFs normally target vascular endothelial growth factor (VEGF) [58, 59] under low oxygen tension [60] up-regulating angiogenesis and now do so in pseudohypoxia when *VHL* and *EPAS1* mutations are present. Cluster1 contains mutations harboring metastatic potential with *SDHB* mutations. The association of malignancy and *SDHB* mutation in P-PGL was first noted in 2003 by Gimenez-Rogues et al. [61] in a small cohort. Others have reported the rates of malignancy in *SDHB* mutants of 13–71% [62–68] with *SDHA* and *SDHD* carrying lower malignancy rates of 10–33% and up to

31%, respectively [62, 69]. In contrast, the rate of malignancy in patients with *VHL* and *EPAS1* mutations remains low. In 2017, the WHO defined metastatic disease as classified by the presence of P-PGLs in nonchromaffin organs; from here on the term malignant will be replaced by metastasis. Prior to 2017, unsupervised clustering from other integrative genomic studies of P-PGL cohorts demonstrated clustering of *SDHx* and *VHL* into a single cluster with hypoxic signatures and *RET/NFI* mutants into a second cluster notable for activation of the Ras-mediated mitogen-activated protein kinase (MAPK) pathway [70, 71]. Further subdivision of the first cluster with hypoxic signatures into separate *SDHx* and *VHL* subclusters based on target HIF gene expression with HIF 1- α targets predominantly expressed in *VHL* tumors was noted [70, 71]. The TCGA study demonstrated a subgroup of cluster1 containing *VHL/EPAS1* tumors, however a prior study from 2013 revealed not all *EPAS1* mutated P-PGLs have the same pseudohypoxic profile as *VHL* (and *SDHx*) and may belong in a cluster separate to *VHL* with upregulation of other hypoxia related genes, *PCSK6* and *GNAI4* [72].

Heterogenous secretion of catecholamines is observed in cluster1 with increased levels of normetanephrine, dopamine, and 3-MT measured in many patients [48]. The majority of *SDHB* mutated PGLs secrete norepinephrine or both norepinephrine and dopamine, and 3-MT [73]. Other *SDHB* tumors produce only dopamine [74] while some are biochemically silent [35], lacking the clinical manifestations of excess catecholamines and may present atypically with pain from mass effect or have no symptoms at all. The *SDHB* silent tumors lack TH, the rate-limiting enzyme responsible for the conversion of tyrosine to DOPA in catecholamine synthesis. Cluster2 is the Wnt signaling cluster and contains somatic mutations in all patients presenting with sporadic P-PGLs [50]. Mutations included are cold shock domain containing E1 (*CSDE1*) and mastermind like transcriptional coactivator 3 (*MAML3*). Clinical correlation in the pan-genomic bioinformatic analysis in TCGA database suggested this may be an aggressive cluster with some patients having metastasis and recurrence [48]. Biochemical phenotypes in cluster2 demonstrated both epinephrine and norepinephrine profiles. Cluster3 comprises both germline and somatic mutations involving the kinase signaling pathway such as rearranged during transfection (*RET*), neurofibromin 1 (*NFI*), MYC-associated factor X (*MAX*), transmembrane protein 127 (*TMEM127*), and Harvey rat sarcoma-associated protein (*HRAS*) [48]. The common thread in this cluster involves the dysregulation of the kinase pathway leading to cell growth independent of extracellular signals. Biochemical phenotypes in this cluster demonstrated epinephrine and norepinephrine profiles. A summary of the clusters can be viewed in ► Table 1.

Although the insight into molecular dysregulation in P-PGLs provides a better understanding of tumor pathophysiology, the molecular taxonomy of the above clustering schemes cannot be completely relied upon to direct surgical management of P-PGLs. Currently, clinical features and natural history associated with these mutations such as the rates of metastasis, multifocality, and recurrence guide the surgical management and surveillance. The reported metastasis for mutations in P-PGLs by known mutations are summarized in ► Table 2. Partial adrenalectomy for PHEO is acceptable in cases where benign lesions with high rates of multifocality and recurrence are expected such as in *VHL* and multiple endocrine neoplasia 2 (MEN2) (*RET* mutations) syndromes. However, a more extensive surgical approach such as total adrenalectomy, or a prophylactic

lymphadenectomy should be considered in patients with germline mutations associated with a high rate of metastasis [75].

Biochemical phenotypes

Distinct P-PGL biochemical adrenergic, noradrenergic, and dopaminergic phenotypes arise naturally from the type of catecholamines secreted from these neuroendocrine tumors. PGLs that are non-secretory are classified as silent.

The noradrenergic phenotype includes those tumors that mostly secrete norepinephrine. Assays reveal elevated levels of norepinephrine and normetanephrine. Anatomically, noradrenergic phenotypical P-PGLs are mostly located outside the adrenal gland. However, PHEOs in patients with von Hippel–Lindau syndrome (VHL), can predominantly secrete norepinephrine [76]. The noradrenergic phenotype of *SDHx* mutated P-PGLs is due to epigenetic hypermethylation of the promoter region of the PNMT gene and subsequent downregulation of the enzyme PNMT [54].

Adrenergic phenotypic P-PGLs secrete epinephrine and high levels of metanephrines are assayed. PNMT is the enzyme that converts norepinephrine to epinephrine. Tissues that contain PNMT include the adrenal glands and the organ of Zuckerkandl; found near the origin of the inferior mesenteric artery, as described by Emil Zuckerkandl, but may extend to the aortic bifurcation. Thus, the adrenergic phenotype P-PGLs are found in these locations.

P-PGLs secreting mostly dopamine make up the dopaminergic phenotype and these are mostly HNPGLs associated with succinate dehydrogenase subunit mutations [73]. Some P-PGLs of this phenotype have been reported in the adrenal glands [77]. 3-MT levels should be assayed for this biochemical phenotype.

Imaging

Computed tomography—After P-PGL has been diagnosed biochemically, localization with imaging should be pursued. Practice guidelines recommend computed tomography (CT) with intravenous (iv) contrast as the first line imaging modality [2]. The sensitivity and specificity for localizing P-PGLs with contrast CT is 90 and 93%, respectively [78]. CT sensitivity for bilateral PHEOs is 66% and for extra-adrenal tumors 64% [79]. Modern contrast CT can usually localize lesions greater than 5 mm. See ► Fig. 1 for sample CT.

In patients with known *SDHx* mutations CT imaging of the chest, abdomen, and pelvis should proceed despite biochemical results.

Magnetic resonance imaging—Magnetic resonance imaging (MRI) is another useful imaging modality for P-PGLs. In fact, gadolinium enhanced MRI angiography is the preferred modality for localizing HNPGLs as determined from a multicenter prospective study with the same imaging protocols and a centralized imaging assessment [80]. Sensitivities for MRI, as reported from a retrospective review, are as follows: 98% overall for P-PGLs, 100% for bilateral PHEOs, and 88% for extra-adrenal PGLs [79]. High signal intensity, or “light bulb sign” may be present in up to 30% of PHEO on T2 weighted MRI [81]. Resolution of P-PGLs on MRI is also limited in size similar to CT at about 5 mm.

MRI may be the first line when contraindications to CT with iv contrast are present, or if surgical clips are present causing artifact on CT, or in cases where ionizing radiation should be limited (e. g., pregnant patients, young children, etc.).

Functional imaging—Functional imaging may enhance morphological imaging in specific cases of P-PGLs, such as metastatic disease, hereditary disease, and PHEO larger than 5 cm that have a higher rate of metastasis [82]. Functional imaging may be able to locate disease that is otherwise occult on anatomical imaging studies [79, 83] and assist with preoperative staging and operative planning.

The 2014 Endocrine Society practice guidelines recommended ^{123}I -metaiodobenzylguanidine (MIBG) scintigraphy for metastatic disease localized on anatomic imaging, extra-adrenal disease, tumors of large size, or in patients with suspicious or known metastatic disease to identify candidates for ^{131}I -MIBG ablative therapy [2]. However, the sensitivity of MIBG scintigraphy is inferior to ^{18}F -Flude-oxyglucose (^{18}F -FDG), ^{18}F -FDOPA, and ^{18}F -Fluorodopamine (^{18}F -FDOPAMINE) [84]. Timmers et al. demonstrated near 100% sensitivity for tumor detection in *SDHB* related metastatic disease with ^{18}F -FDG PET/CT which was better than MIBG at 80% sensitivity [84]. Currently, ^{18}F -FDG PET/CT is widely available and less costly when compared more modern radiopharmaceuticals such as ^{68}Ga -DOTATATE. The 2016 European Society of Endocrinology Clinical Practice Guidelines recommended ^{18}F -FDG PET/CT to screen for metastatic disease preoperatively in patients with P-PGLs with elevated 3-MT or in patients with *SDHB* germline mutations [85].

Considering the aforementioned TCGA clustering scheme for P-PGLs, functional imaging phenotypes have resulted. For cluster1 TCA subgroup, superior lesion detection via functional imaging is obtained with ^{68}Ga -DOTATATE PET/CT, with 98.6% detection rate [83, 86, 87]. The affinity for ^{68}Ga -DOTATATE tracer is due to the high expression levels of somatostatin type 2 receptors in these tumors. See ► Fig. 2 for *SDHB* P-PGL and comparison of ^{18}F -FDOPA and ^{68}Ga -DOTATATE PET/CT images. Best lesion detection with functional imaging for cluster1 VHL/EPAS1 subgroup is via ^{18}F -DOPA PET/CT [37, 38]. Optimal functional imaging for cluster2 is yet to be determined while cluster3 is best imaged functionally with ^{18}F -DOPA PET/CT [88]. The high detection rate in metastatic or extra-adrenal PGL disease with these radiopharmaceuticals in PET/CT are invaluable in precise surgical planning to a Now the surgeon to accurately plan the extent of surgery and the surgical approach.

Pre-operative management—Prior to transferring a patient with P-PGL to the operating room for resection of their tumor(s), it is recommended by many experts in the field [89] and by guidelines [2], that the patient should have 7–14 days of alpha-adrenergic blockade for hormonally active P-PGLs. Randomized controlled trials to support the use of pre-operative alpha-blockade do not exist. Successful resection of P-PGL has been reported without pre-operative alpha-adrenergic blockade [90–93], but it is not the practice at most institutions. The goal of pre-operative alpha-blockade is to decrease hypertension and decrease the chance of hypertensive crises intra-operatively, while decreasing morbidity. Expert opinion supports alpha-adrenergic receptor blockade with the blood pressure

goals of 130/80 mmHg and not less than 80/45 mmHg while sitting [94], with less stringent goals if not tolerated by the patient. Patients who present with P-PGL crisis should be admitted to hospital for aggressive medical management of symptoms before surgical intervention [95]. Hemodynamically labile patients with refractory hypertension may require a multidisciplinary team for pre-operative stabilization. It is our practice to perform a pre-operative cardiovascular evaluation with an electrocardiogram (EKG). An EKG may be sufficient in younger, otherwise healthy, patients. In older patients, or patients with longstanding hypertension, or with pre-existing cardiac disease a transthoracic echocardiogram is performed. A cardiologist may be consulted to offer an evaluation of the patient if suspicious findings are noted or pre-existing cardiac comorbidities are known. Patients with other pre-existing comorbidities may require a more extensive pre-operative evaluation. First line medical therapy includes both nonselective alpha-adrenergic receptor blockers such as phenoxybenzamine and selective alpha (α) 1 adrenergic receptor blockers such as doxazosin, prazosin, and terazosin. A retrospective study of 44 patients with PHEO who underwent adrenalectomy showed there was no clinically relevant difference among patients blocked pre-operatively with either phenoxybenzamine or doxazosin in regards to hemodynamics intra-operatively (200/110 mmHg; 40% for doxazosin vs. 22% for phenoxybenzamine, $p = 0.28$) or with hypotension post-operatively ($<90/60$ mmHg; 48% for doxazosin vs. 43% phenoxybenzamine, $p = 0.56$) [96]. Signs and symptoms that suggest adequate α -blockade include mild postural hypotension and nasal stuffiness. Patients may experience fatigue, nausea, indigestion, and sedation with α -adrenergic receptor blockade.

Second line medical therapy includes calcium channel blockers (CCBs). CCBs decrease vascular smooth muscle tone by limiting cellular calcium influx and minimize coronary artery vasospasm. If α -adrenergic receptor blockade alone is not adequate, CCBs may be used in combination therapy. CCBs may also be used alone if the patient is normotensive, or mildly hypertensive.

Classical teaching is to use α -adrenergic receptor blockers prior to administering beta(β)-adrenergic receptor blockers, which help control tachyarrhythmias, to avoid unopposed α stimulation and possible hypertensive crisis. Either selective or nonselective β -blockade may be used with expert opinion supported heart rate goals 60–70 beats per minute [94].

Metyrosine inhibits catecholamine synthesis by competitive inhibition of TH. Metyrosine is typically used in combination with α -adrenergic receptor blockers to help combat refractory hypertension [97].

Additional pre-operative preparation includes restoring the intravascular blood volume after initiation of α -adrenergic receptor blockade with a high salt diet for three days before surgery, or via administration of 1–2 liter of iv normal saline the day before the operation. Careful salt or fluid intake should be adhered to for patients with renal or cardiac comorbidities. Expanding the blood volume may aid in mitigating hypotension after the adrenergic stimulus has been removed in the post-operative period, although only retrospective data exists to support the practice [94].

It should be noted that no pre-operative therapy to date has been able to completely eliminate intra-operative hemodynamic swings.

Intra-operative management—Successful operative resection of pheochromocytoma requires intra-operative communication between the surgeon and anesthesiologist. Before surgery, a detailed operative plan should be outlined. The anesthesiologist needs to be prepared to manage labile blood pressure. The most commonly used intra-operative anti-hypertensive agent in patients with PHEO is esmolol. For refractory hypertension, magnesium sulfate infusion can be given. Advantages associated with magnesium are that it is inexpensive, widely available and safe for use in pregnancy [98]. After tumor excision, hypotension may occur, which is treated primarily with isotonic iv fluids and, if needed, with bolus or infusion of ephedrine or phenylephrine.

Arrhythmias and exacerbation of hypertension can occur during intra-operative tumor manipulation. Tumor manipulation should be discontinued until resolution of hypertension; however, pharmacologic agents may also be needed.

Adequate iv access with large-bore peripheral or central venous catheters should be obtained prior to surgery. In addition, a radial arterial line is typically inserted for hemodynamic monitoring. Pulmonary artery (Swan–Ganz) catheterization is no longer routinely utilized. Depending on tumor size, location, and anticipated blood loss, it may be necessary to cross-match blood products for transfusion.

Surgical management—Surgery remains the mainstay of treatment for P-PGL and offers the best chance for cure or remission. Precision surgery can be offered on an individual basis once a patient's P-PGL has been fully characterized through biochemical testing, genetic testing, anatomic imaging, and functional imaging as indicated. Surgery recommendations from practice guidelines [2] currently suggest laparoscopic adrenalectomy for most PHEOs and open surgery for PHEO > 6 cm or invasive PHEO to achieve complete (R0) resection. Guidelines also recommend open surgery for PGL but minimally invasive (MI) techniques may be used for small non-invasive tumors in favorable locations [2]. To date there are no randomized controlled trials comparing open to MI resection of P-PGLs.

Minimally invasive surgery—MI techniques for the resection of benign PHEO and select PGLs is the standard of care [2]. Several MI techniques are in use today including transperitoneal and retroperitoneal laparoscopic approaches, as well as robotic resection of P-PGLs. The MI technique and approach chosen is at the surgeon's discretion with regard to their expertise, preference, or which MI technique best suits each case.

As previously stated Dr. Gagner was the first to report on laparoscopic transperitoneal adrenalectomy for PHEO. Since his account, it has become the gold standard for PHEOs up to 6 cm in size [2] that have a low likelihood of metastasis. At our institution suspected benign PHEO larger than 6 cm are routinely resected with a transperitoneal laparoscopic approach with good outcomes [42]. Other authors have published their experience with laparoscopic resection of benign PHEO up to 13 cm and concluded that safe and effective outcomes can be achieved [99]. Additionally, a multicenter retrospective review comparing

laparoscopic adrenalectomy, performed by three endocrine surgeons and one minimally invasive surgeon, for PHEO < 6 cm and ≥ 6 cm (including three tumors > 10 cm with largest tumor 14.5 cm) demonstrated that there was no statistically significant difference in the two groups complication rates, postoperative biochemical cures, or tumor recurrence rates and concluded that laparoscopic adrenalectomy could be safely performed for PHEO regardless of size, when carefully selected, by an experienced surgeon [100]. Laparoscopic surgery has significant advantages over the traditional open approach, including smaller incisions, reduced pain, shorter hospital length of stay, faster recovery, and a lower rate of wound complications [101]. Although some PGLs in favorable locations can safely be resected laparoscopically [102], the choice between open surgery or MI approaches should be based on the risk of regional metastasis in each patient with PGLs. Because the oncologic outcome of MI resection in patients with high risk for metastatic P-PGLs is not well proven, an open resection with or without lymphadenectomy should be considered as a gold standard.

In contrast, patients with germline mutations known to have low-risk of metastasis, are candidates for MI resection. MI partial adrenalectomy is recommended for patients with *VHL* and *RET* mutations [103] which represent von Hippel–Lindau (VHL) syndrome and multiple endocrine neoplasia type 2 (MEN2) syndromes. These patients have a high likelihood (40–50% in VHL [104], > 50% in MEN2 [105–107]) of developing bilateral PHEOs either synchronously or metachronously and the chance of metastasis is very low. The surgical goal is to leave enough adrenal cortex, about 30%, with a preserved adrenal vein in situ to prevent adrenal insufficiency and avoid life-long steroid replacement therapy [105]. Castinetti et al. performed a large multicenter, multi-continent retrospective study of patients with MEN2 syndrome status post adrenalectomy for PHEO and included in their cohort results of partial adrenalectomy. The patients with MEN2 syndrome and PHEO undergoing partial adrenalectomy had 3% recurrence in the operated gland compared to 2% undergoing total adrenalectomy, with no statistical difference in recurrence between the two surgical techniques [105]. In their cohort, 57% of patients who underwent bilateral partial adrenalectomy for PHEO remained steroid independent [105]. Others report about 90% of patients can remain steroid independent [103, 108] after partial adrenalectomy for benign heritable PHEO. Approximated PHEO recurrence rates are 10–15% over 10 years for patients with VHL [108, 109]. The cumulative PHEO recurrence rate for patients with MEN2 syndromes after partial adrenalectomy at 5 and 10 years is 38.5%, including ipsilateral and contralateral gland recurrence [110]. For sporadic PHEO or other PHEO mutations with a decreased likelihood of bilateral disease and or higher chance of metastasis total adrenalectomy is preferred.

Robotic adrenalectomy has similar outcomes to laparoscopic adrenalectomy. Some authors argue that robotic surgery for P-PGL is useful for larger tumors, truncal PGLs, and bilateral and partial adrenalectomies offering additional degrees of freedom, especially useful in a limited operative spatial envelope as compared to laparoscopy. However, the cost associated with robotic surgery is higher than laparoscopy [111].

Laparoscopic adrenalectomy is also feasible in obese patients with PHEO. A study examining transperitoneal laparoscopic adrenalectomy (including 119 patients with PHEO) outcomes in obese patients demonstrated no statistical differences in patients stratified by

BMI from normal to morbidly obese in regards to operative time, intra-operative blood loss, the total length of hospital stay, morbidity rate and 30-day readmission rate [112]. A recent retrospective multicenter study comparing hemodynamic instability in 341 patients undergoing either transperitoneal laparoscopic or retroperitoneoscopic adrenalectomy for PHEO revealed statistically significant differences after multi-variate analysis in hemodynamics related to surgical approach; with retroperitoneoscopic adrenalectomy demonstrating decreased intra-operative mean arterial pressure (MAP) (<60 mmHg) (odds ratio 6.255, 95% confidence interval (CI) 1.134–34.235, $p = 0.035$) when compared to the intra-operative MAP of transperitoneal approach [113]. Another retrospective multicenter analysis showed factors predicting postoperative morbidity of laparoscopic adrenalectomy for unilateral PHEO in 225 patients were related to older age (mean age of 55 vs, 49, $p = 0.045$), greater mean size of tumor (5 cm vs. 4.2 cm, $p = 0.032$), and greater mean number of pharmacologic agents used for pre-operative management of hypertension ($p = 0.025$), and pre-existing coronary artery disease ($p = 0.008$) (CAD) [114]. The same authors also found past medical history of CAD [OR (95% CI) = 14.41; (3.119–66.57)], female sex [OR (95% CI) = 12.05; (1.807–80.31)], and incidence of intra-operative hemodynamic instability episodes (both SBP ≥ 200 mmHg and MAP<60mmHg) [OR (95% CI) = 4.13; (1.009–16.90)] remained independent predictors for postoperative cardiovascular morbidity [114].

Open surgery—Open surgery or laparotomy is chosen when faced with metastatic [115] or high risk for metastatic disease (e. g., *SDHB* mutations) disease, or for multifocal lesions where a laparoscopic approach may not be feasible. Additionally, guidelines recommend open techniques for lesions > 6 cm [2]. Although reoperation is not a contraindication for MI resection, reoperation for recurrence may be best served with an open approach and complications maybe higher in reoperative cases. Resection of the primary lesion in metastatic disease has been shown to improve overall survival (OS) and reduce tumor burden and the associated sequelae of excess catecholamines [116]. However, cytoreductive procedures are not likely to result in a durable, clinically significant biochemical response [117]. If curative surgical resection cannot be performed, cytoreductive surgery may still be considered as it can improve the efficacy of other therapeutic options such as targeted radiotherapy [118]. Patients with disease confined to the abdomen were more likely to achieve and maintain a biochemical response postoperatively than those with extra-abdominal disease [117]. Metastases occur primarily in lymph nodes, bone, liver, and lung, with the highest rate (80%) occurring in lymph nodes [119]. Because of this preferential spread to lymph nodes, surgery includes locoregional lymphadenectomy at the time of laparotomy in addition to resection of the primary tumor, particularly in patients with high-risk for metastasis such as *SDHB* germline mutations [42, 63, 120]. Multiple primary PGLs within the abdomen are often indistinguishable clinically from metastatic disease to aortocaval lymph nodes and thus, lymphadenectomy should be performed. For lesions that are difficult to locate because they are small, or the patient has abundant scar tissue from previous surgery intra-operative ultrasound is used regularly at our institution for intra-operative localization with good success. Measurement of gamma radiation from ^{68}Ga -DOTATATE has been used at the time of surgery to locate P-PGLs exploiting the

affinity of the expressed somatostatin type 2 receptors for 68-Ga-DOTATATE with 81% sensitivity in a small cohort [121].

Head and Neck paragangliomas—Traditionally, surgical resection was considered as the first line therapy for most CBTs but as more information has been incorporated to more comprehensively characterize CBTs such as mutational status with risk of metastasis, tumor biology, growth rate, tumor size, patient age and condition, and operative morbidity the management has shifted from more selective operative management to wait-and-scan. Ellis et al. [122] demonstrated that CBTs with *SDHB* mutation should be resected while cases not positive for *SDHB* mutation may adopt an active surveillance plan unless lesions are symptomatic, size ≥ 2 cm, and/or biochemically active. A patient presenting with multifocal disease including HNPGL and disease outside the neck should have the extra-cervical lesions resected prior to approaching the HNPGLs.

HNPGLs associated with cranial nerves are often best followed with active surveillance if asymptomatic and may be treated with external beam radiation with local control achieved in 79–100% of cases [123]. The largest meta-analysis to date of observational and retrospective studies (no randomized controlled trials exist for these rare tumors) for the surgical resection of > 4000 CBTs showed that Shamblin classification [124] was a risk factor for complications including cranial nerve injury [3.76% (95% CI 2.62–5.35) for Shamblin I CBTs, 14.14% (95% CI 11.94–16.68) for Shamblin II, and 17.10% (95% CI 14.82–19.65) for Shamblin III], and CVA (Shamblin I: 1.89% CVA rate (95% CI 0.92–3.82), Shamblin II: 2.71% (95% CI 1.43–5.07), Shamblin III: 3.99% (95% CI 2.34–6.74)] [28]. Overall CVA rate was 3.5%, cranial nerve injury persisting beyond thirty days after resection was 11.5%, and preoperative embolization did not reduce postoperative cervical hematoma [28]. Another study of 20 resected CBTs showed that cranial nerve injury was more likely to occur during resection of high riding CBTs as determined on preoperative imaging (superior tip of C2 dens to superior border of CBT = 1.8 vs. 2.9 cm, $p < 0.01$) [125].

Options for reducing tumor burden with hepatic metastases include liver-directed therapy, wedge resection of lesions, or anatomic hepatectomy. Resection of liver metastases can help alleviate or reduce symptoms of catecholamine excess and improve survival for lesions with Ki-67 index $< 20\%$ [126]. An additional option for hepatic lesions includes radiofrequency ablation which can be performed in tandem with surgery or postoperatively percutaneously. Transarterial chemoembolization (TACE) has been shown to reduce metastatic deposits as well.

Other options beyond cytoreductive surgery for metastatic P-PGL for the reduction of tumor burden and palliation of symptoms which have shown efficacy include radiofrequency ablation, cryoablation, and percutaneous ethanol ablation [127].

Postoperative management—The most common post-operative complications are hypotension and rebound hypoglycemia. Blood pressure, heart rate, plasma glucose levels, and urine output should be monitored for 24–48 h; at our institution, patients are routinely admitted in the intensive care unit for at least 24 h after surgery. Acute post-operative hypotension is usually due to the expansion of the intravascular space and, therefore,

treated with isotonic fluid and, rarely, vasopressors, if needed. Adrenal insufficiency should be treated with exogenous steroid replacement therapy if no adrenal tissue remains after surgery. Close monitoring for adrenal insufficiency is necessary in patients who underwent bilateral partial adrenalectomies, and partial adrenalectomy for only one remaining adrenal gland. An ACTH stimulation test may be used to assess stress response and guide post-operative steroid replacement therapy.

Follow up—Postoperative patients should have adequate follow up as suggested by the 2016 European Society of Endocrinology Practice Guidelines [85]. Two to six weeks after surgery patients with preoperative elevated catecholamines should have postoperative levels of metanephrines, normetanephrine, or 3-MT assayed depending on which values were elevated preoperatively. For patients that were biochemically silent with elevated CgA this biomarker level should be checked two to six weeks postoperatively. Elevated levels of catecholamine metabolites or CgA may suggest persistent or recurrent disease [85].

Imaging should be performed at 3 months postoperatively in patients with elevated catecholamine metabolites or CgA, or in patients with a preoperative biochemically silent disease.

Surveillance should include annual measurement of plasma or urinary metanephrines and 3-MT for P-PGL that were active biochemically before resection. Imaging should be performed if positive biochemical values are observed.

In biochemically silent cases CgA should be measured annually. Anatomical and functional imaging studies, when appropriate, should be performed every one to two years. Surveillance in low-risk patients with P-PGL is carried out for 10 years and surveillance is life-long for high-risk patients (young age at presentation, inherited syndromes, large tumors, and paragangliomas).

Conclusion

Tremendous advances in our understanding of the underlying pathogenesis, diagnosis, genetics, molecular machinery of mutated pathways, and imaging of P-PGLs have been made that help guide precise and more personalized surgery of P-PGLs. Future study will hopefully allow the provider to predict metastasis of these complex endocrinopathies before surgical intervention.

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Fig. 1.
Computed tomography images **a** and **b** and magnetic resonance images **c** and **d** of pheochromocytoma **a** and **c** and paraganglioma **b** and **d**. α : Pheochromocytoma, arrows: Paraganglioma.

Fig. 2. ¹⁸F-FDOPA PET/CT **a** and ⁶⁸Ga-DOTATATE PET/CT **b** in patients with *SDHB* germline mutation and left pheochromocytoma and right neck and intra-abdominal paragangliomas.

Table 1

Clustering Schemes for pheochromocytoma and paraganglioma.

P-PGL Clusters	Mutations	Most Common Locations
1. Pseudohypoxia		
TCA related	<i>SDHA, SDHB, SDHC, SDHD, SDHAF2, FH</i>	skull base to pelvis
VHL/EPAS-1 related	<i>VHL, EPAS-1</i>	abdominopelvic
2. Wnt Signaling	<i>CSDE1, MAML3</i>	abdominopelvic
3. Kinase Signaling	<i>RET, NET MAX, TMEM127, HRAS</i>	abdominopelvic

Table 2

Pheochromocytoma and paraganglioma mutations and reported metastasis.

Mutation	Metastasis (%)	Metastasis in Cohort(s) n/N [Ref]
<i>RET</i>	0–4.1	0/85 [107], 2/563 [105], 1/228 [128], 1/206 [106], 2/49 [62]
<i>VHL</i>	1.1–7.7	3/273 [104], 2/48 [129], 6/78 [62]
<i>SDHB</i>	12.6–71.4	11/87 [65], 40/295 [66], 126/611 [62], 5/24 [129], 27/48 [63], 85/143 [64], 59/88 [67], 15/21 [68]
<i>SDHD</i>	0–31.3	0/34 [130], 4/130 [131], 2/47 [129], 2/26 [132], 20/64 [62]
<i>SDHA</i>	10.0–33.3	3/30 [133], 4/34 [134], 1/4 [135], 2/6 [136]
<i>SDHC</i>	0–27.7	0/8 [137], 5/18 [138]
<i>SDHAF2</i>	0	0/1 [134], 0/2 [139], 0/16 [140]
<i>NFI</i>	0–11.5	0/234 [141], 0/9 [142], 3/41 [143], 17/148 [144]
<i>EPAS1</i>	0	0/5 [145]
<i>FH</i>	60	3/5 [53]
<i>MAX</i>	9–12.5	1/11 [134], 2/16 [146]
<i>TMEM127</i>	5–10	1/20 [147], 3/29 [134]
<i>HRAS</i>	0–7.7	0/21 [148], 1/17 [48], 1/13 [149]
<i>MAML3</i>	25	2/8 [48]
<i>CSDE1</i>	0	0/4 [48]