



Published in final edited form as:

Ann Surg Oncol. 2020 May ; 27(5): 1338–1347. doi:10.1245/s10434-020-08221-2.

Update on Pheochromocytoma and Paraganglioma from the SSO Endocrine and Head and Neck Disease Site Working Group, Part 2 of 2: Perioperative Management and Outcomes of Pheochromocytoma and Paraganglioma

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Abstract

This is the second part of a two-part review on pheochromocytoma and paragangliomas (PPGLs). In this part, perioperative management, including preoperative preparation, intraoperative, and postoperative interventions are reviewed. Current data on outcomes following resection are presented, including outcomes after cortical-sparing adrenalectomy for bilateral adrenal disease. In addition, pathological features of malignancy, surveillance considerations, and the management of advanced disease are also discussed.

PERIOPERATIVE CONSIDERATIONS

Patients who undergo PPGL resection may exhibit labile blood pressure (BP), arrhythmias, and tachycardia in the perioperative period. Relatively small retrospective observational studies of patients undergoing surgery for PPGL have not reported intraoperative deaths but have reported arrhythmias, sustained hypertension and/or hypotension, postoperative myocardial infarction, stroke, and prolonged intubation.¹⁻³ Significant risk factors

include large tumor size, increased levels of preoperative catecholamines, preexisting catecholamine-induced heart failure, and lengthy complicated surgery.^{2,3} Therefore, management of PPGL should be multidisciplinary, including experienced surgeons, anesthesiologists, and endocrinologists.

PREOPERATIVE BLOCKADE

The goals of preoperative management include control of hypertension and normalization of intravascular volume. Clinical institutional practices vary with no universally accepted algorithm. Preoperative readiness is assessed by orthostatic BP measurements, aiming for a seated blood pressure of 120–130/80 mmHg, a standing systolic blood pressure (SBP) 90 mmHg, and a heart rate between 60 and 70 beats/min (bpm) seated and 70 to 80 bpm standing. Patients should also be well hydrated and have a high-sodium diet prior to surgery.³ No data exist on optimal duration of preoperative treatment, but a minimum of 7 days is advised.

Alpha-selective or nonselective blockade is the most common approach to preoperative preparation of patients with PPGL and is always initiated first, with the addition of beta blockade as needed for tachycardia after at least 3–4 days of alpha blockade administration because unopposed alpha-adrenergic stimulation can lead to worsening of hypertension. Calcium channel blockers (CCBs) are used to supplement alpha and beta blockade or as an alternative. Metyrosine is typically reserved for patients who cannot tolerate alpha blockers or have alpha receptor and CCB-refractory hypertension,⁴ and recent data suggest that its use may be associated with improved cardiovascular outcomes in combination with a nonselective alpha blockade⁵ (Table 1).

Alpha blockade is most commonly achieved with phenoxybenzamine, a nonselective irreversible blocker of alpha receptors; or a selective reversible alpha-1 antagonist such as doxazosin, prazosin, and others. Several retrospective papers have addressed the superiority of one strategy versus the other, which have not shown a difference in increased complications.^{6,7} A recent prospective open-label randomized trial comparing selective and nonselective alpha blockade did show phenoxybenzamine as more effective at preventing intraoperative hemodynamic instability but no difference in clinical outcome.⁸ Phenoxybenzamine is currently extremely expensive in the USA and has a high side-effect profile. In practice and depending on local preference, the surgeon, the endocrinologist, or the hypertension expert initiates the oral alpha blockade (Table 1). The patient should have access to a blood pressure cuff at home and record a minimum of twice daily blood pressure and heart rate measurements. After 2 or 3 days, the alpha blocker dose is then increased to target a systolic blood pressure consistently at or below < 130 mmHg. Beta blockade is added if the pulse rate is consistently > 100 bpm. Tachycardia is less common when a selective reversible alpha blocker is used,⁹ but it is often necessary when the nonselective alpha blocker phenoxybenzamine is utilized. If the patient does not have the diagnosis of hypertension, the patient should still be blocked starting with a low-dose alpha blocker.

THE PREGNANT PATIENT

In a gravid patient, the goal is to prevent extreme hemodynamic fluctuations. No data exist on optimal blockade drug or its duration,^{10,11} but phenoxybenzamine, betablockers, CCBs, and doxazosin have all been used safely.^{12,13} The importance of balance between hypertension control and adequate uterine perfusion is vital.^{14,15} Maternal deaths have been reported as high as 48%, but with earlier diagnosis and appropriate perioperative care, mortality is as low as 2%.^{12,14} The optimal timing of PPGL resection is the second trimester, with minimally invasive techniques if feasible. Alternatively, a concomitant planned c-section and PPGL resection can be performed, or resection can be performed in the medically well-controlled patient in the postpartum period.¹⁶

MANAGEMENT BY ANESTHESIA

Intraoperative communication between surgeons and anesthesiologist is vital. Patients require adequate IV access and an arterial catheter for continuous blood pressure monitoring. A discussion of the anesthetic management of PPGL is beyond the scope of this review, but the anesthesia team should ideally be experienced with the management of such complex cases.

PERSONALIZED SURGICAL MANAGEMENT

Surgical approaches for adrenalectomy include both minimally invasive (laparoscopic or robotic) and open techniques (Table 2). The guiding principles include early identification and ligation of the adrenal vein, and minimal manipulation of the tumor to prevent tumor rupture and intraoperative release of catecholamines with subsequent blood pressure lability.¹⁷⁻¹⁹ Studies have shown improved outcomes when resection is performed by advanced laparoscopic surgeons and high-volume adrenal surgeons (> 4–6 adrenalectomies/year).²⁰⁻²³

Minimally invasive (laparoscopic or robotic) adrenalectomy has become the standard of care for the majority of patients with pheochromocytomas. This approach may be performed with either the transabdominal (TA) or posterior retroperitoneoscopic (PRA) approach.^{19,24-29} The choice of approach depends on surgeon preference and familiarity with the techniques, as well as factors such as patient body habitus/body mass index (BMI), indications for surgery, tumor characteristics, size and location, and history of prior abdominal or retroperitoneal procedures that may influence the decision.²⁴⁻²⁹

The minimally invasive TA approach is familiar to most surgeons and may allow for easier conversion to open if necessary. TA can be performed in patients with prior upper abdominal surgery (ipsilateral or contralateral to the adrenal). However, adhesions may add to the complexity and length of the case.³⁰ The PRA approach provides direct access to the adrenal gland, without the need for mobilization or adhesiolysis.²⁴⁻²⁷ In a study of 46 patients with similar demographics and tumor characteristics undergoing adrenalectomy for pheochromocytoma (23 TA and 23 PRA), PRA was associated with shorter operative times (99.9 vs. 144.8 min; $p > 0.001$), estimated blood loss (8.4 vs. 123.8 mL; $p = 0.02$), and postoperative length-of-stay (1.9 vs. 3.1 nights; $p < 0.01$).²⁶ The study suffered from

selection bias, since the PRA approach was associated with smaller tumors. PRA has been shown to be safe in children as well.³¹ Other benefits of PRA include the ability to perform bilateral adrenalectomy without repositioning. However, this must be balanced by potential limitations, including a “cognitive reorientation” of anatomical landmarks and appropriate patient selection based on body habitus and tumor size/location in relation to the kidney and its hilum. Typically, it is best for tumors < 6 cm located posterior and superior to the kidney in patients with little retroperitoneal fat^{24-26,28} (Fig. 1).

Robotic-assisted adrenalectomy, using both TA and PRA approaches, has been described for benign tumors, including pheochromocytoma.³²⁻³⁵ Advantages of robotic adrenalectomy include ergonomics, three-dimensional visualization, and improved wrist articulation and degrees of freedom allowing for greater surgical precision. Relative disadvantages include cost, a possible learning curve, and the lack of haptic feedback.³²⁻³⁵ Although a recent report showed similar costs and slightly faster procedure times for RA versus LA in a high-volume center.³⁶ The robotic PRA can be hampered by the small access window which can inhibit robotic arm movement with currently available systems.

Open resection remains the standard of care when there is clinical concern for malignant/invasive PPGLs or with large tumors at risk for rupture. The prevention of tumor rupture is important to avoid local recurrence or pheochromocytomatosis, especially given the few effective systemic therapies for metastatic pheochromocytoma.¹⁹ Furthermore, open adrenalectomy may be preferred in patients with *SDHB*, *TMEM127*, or *FH* germline mutations, since these mutations are associated with a higher risk of extraadrenal disease, metastatic disease, and recurrence compared with germline mutations in *NFI*, *RET*, or *VHL*.³⁷

Cortical-sparing (partial) adrenalectomy consists in resection of the adrenal pheochromocytoma with preservation of as much normal adrenal as possible to preserve a functioning gland. Cortical-sparing adrenalectomy is offered to patients with syndromic diseases such as multiple endocrine neoplasia type 2 (MEN2) or von Hippel–Lindau disease (VHL) (Fig. 2). This approach has been demonstrated to prevent postoperative adrenal insufficiency in up to 90% of patients,^{19,37-39} although the exact amount of remnant adrenal gland required is unknown.

IMMEDIATE POSTOPERATIVE PERIOD

After monitoring in the recovery room, most patients, if they have an uneventful intraoperative course and are hemodynamically stable, can be admitted to a floor bed. A monitored bed or intensive care unit stay may be required if there is a need for telemetry, hemodynamic monitoring, or the need for ongoing pharmacologic hemodynamic support.

Two potential postoperative complications are hypotension and rebound hypoglycemia.^{40,41} Transient episodes of postoperative hypotension are common. Postoperative hypotension is attributed to a combination of: (1) residual preoperative alpha blockade with an abrupt fall in circulating catecholamines, (2) residual effects of long-acting non-alpha-blocker antihypertensive medications, and (3) hypovolemia due to preoperative volume contraction

and intraoperative blood loss. Treatment includes aggressive IV fluid boluses for volume resuscitation. If postoperative hypotension persists with adequate fluid resuscitation, about 10% of patients may transiently require IV vasopressors (e.g., phenylephrine, ephedrine, norepinephrine).^{9,17,42}

A relatively rare event after PPGL resection includes rebound insulinemia and hypoglycemia, which typically occurs within the first 4 h postoperatively.⁴⁰ The high preoperative levels of catecholamines causes suppression of alpha and beta cell pancreatic function, which results in insulin resistance and increased liver glycogenolysis.⁴³⁻⁴⁵ In addition, preoperative glycogenolysis is no longer present, the hepatic glycogen stores are depleted, and glucagon release is impaired.^{40,46} Finally, improved peripheral insulin sensitivity with increased uptake of glucose by skeletal muscle contributes to hypoglycemia.⁴⁷ Reported incidence rates of 5–15% are largely limited to case reports and a few retrospective studies.^{45,46,48} Patients with higher preoperative urinary metanephrines/ catecholamine levels are at higher risk.^{45,46} Patients should have regular glucose monitoring (at least every 6 h) and receive 5% dextrose-containing fluids until tolerating oral intake.^{45,49} Insulin requirements should be readjusted for those with preoperative diabetes mellitus.⁴

OUTCOMES

Adrenal Remnant Recurrence in the Setting of Familial Syndromes (MEN and VHL)

Patients with familial syndromes such as MEN 2A, MEN 2B, and VHL may benefit from cortical-sparing adrenalectomies to prevent steroid dependency (Fig. 2). This benefit must be balanced with the risk of tumor recurrence in the remnant adrenal gland; for VHL patients, the estimated risk of recurrence is 10–15% over 10 years with a cortical-sparing approach,⁵⁰ while it has been reported to be as high as 39% for MEN2 patients.⁵¹ A recent series of 96 patients with hereditary pheochromocytomas reported a 3-year recurrence rate of 7% and steroid independence rate of 78%.³⁹

In a large retrospective observational study encompassing 30 medical centers and 563 patients with MEN2 associated pheochromocytomas, 21% of patients ($n = 114$) underwent cortical sparing adrenalectomy, whereas 79% ($n = 438$) underwent total adrenalectomy.⁵² When recurrence was analyzed by operated gland, 4 (3%) out of 153 cortically spared glands had an ipsilateral recurrence with a mean follow-up of 10 years. In comparison, 11 (2%) of 717 total adrenalectomy glands recurred within the adrenal bed with a mean follow-up of 14.2 years. The rate of steroid dependency for patients who underwent either unilateral or bilateral cortical-sparing adrenalectomy was 43%. Of note, patients with at least one-third of an adrenal gland remnant were not steroid dependent.

Outcomes for patients with VHL undergoing cortical-sparing adrenalectomy are equally encouraging. Twenty-six patients with VHL seen at the National Institutes of Health (NIH) over an 8-year period underwent 36 partial adrenalectomies. With a median follow-up of 9.25 years (5–46 years), no patients developed metastatic pheochromocytoma, 11% of patients developed recurrences within the ipsilateral adrenal gland remnant, and 11% of patients developed a pheochromocytoma within the contralateral adrenal gland, requiring partial adrenalectomy, and only 11% of patients became steroid dependent.⁵

RESOLUTION OF HYPERTENSION/CARDIAC MORBIDITY AND DIABETES

Previous studies report that pheochromocytomas increase cardiovascular morbidity and mortality. A retrospective case-control study examining cardiovascular events (myocardial infarction, stroke, or angina pectoris) 5 years prior to diagnosis between patients with pheochromocytomas ($n = 109$) matched to a control group of patients with essential hypertension ($n = 183$) showed a 14-fold increased risk for patients with pheochromocytomas.⁵³ Timmers and colleagues studied the outcomes of 64 patients undergoing surgery for presumably benign pheochromocytoma. Most patients (64%) showed a decrease in blood pressure, but only one-third of patients became normotensive.⁵⁴ Although hypertension may not be cured by surgical resection, surgical resection likely provides cardiovascular benefit. However, long-term data evaluating the outcome of patients with surgically treated PPGL have shown that such patients have a higher mortality compared with the general population. Khorram-Manesh and colleagues followed 121 patients after adrenalectomy for an average of 15 years and found 8 patients to have a recurrence at a mean follow-up of 8.5 years. Of those eight patients, two had a local recurrence, five had a distant recurrence, and one patient had both local and distant recurrences. Half of those patients eventually succumbed to their disease. When comparing the mortality of patients with pheochromocytoma with the general Swedish population, 42 patients with pheochromocytoma died compared with an estimated 23.6 expected deaths. Preoperatively, 86% of the cohort had hypertension, and although there was improvement at 1 year after resection, half of all patients with pheochromocytoma were still hypertensive. Although patients did not have a high recurrence rate and mortality was low, patients had a long-term increased risk of death compared with the general population.⁵⁵ An estimated 15–35% of patients with PPGLs have diabetes and/or impaired glucose tolerance. Beninato and colleagues reported the outcomes of 153 patients with PPGL, of whom 36 patients had diabetes. After surgery, 78.6% of patients had complete resolution and 93.0% had improvement of their diabetes.⁵⁶

RISK OF OVERALL RECURRENCE AND MALIGNANCY

After diagnosis and treatment of a PPGL, patients require lifelong follow-up due to the risk of recurrence and malignancy. A retrospective study by Schovanek and colleagues showed that patients with PPGLs greater than 4.5 cm were at a significantly higher risk of developing metastatic disease. In addition, patients with tumors greater than 5.5 cm had an overall worse survival compared with smaller tumors. The age of initial diagnosis was also found to be an independent predictor of survival.⁵⁷ Recurrence rates have been reported from 2.0 to 6.5% in patients with presumably benign PPGLs.⁵⁸⁻⁶⁰ These recurrences can happen decades later, and therefore, these patients require lifelong biochemical follow-up.

In a large cohort of patients spanning 55 years seen at the Mayo Clinic, 272 out of 3280 patients (8.3%) were found to have malignant PPGLs. Nearly two-thirds of those patients developed metachronous metastases at a median of 5.5 years (range 0.3–53.4 years), and the 5-year overall survival rate for patients with malignant PPGLs was 85.4%. Hamidi and colleagues reported genetic mutations as well in this series, but given the long time span, it was difficult to draw conclusions.⁶¹ Patients that were initially considered with benign

sporadic disease may develop malignancy. Goldstein and colleagues reported an overall malignancy rate of 13%, which reemphasizes the need for lifelong follow-up.¹ Dhir and colleagues assessed clinical factors associated with malignancy in patients with PPGLs and identified patients who are younger, have larger tumors, paragangliomas, and positive genetic testing to have a higher risk of malignancy.⁶²

The outcome of patients with hereditary PPGLs who have a germline mutation in the succinate dehydrogenase subunit B (*SDHB*) (see Part 1 of this review) differs from those patients with sporadic PPGLs. Patients with *SDHB* mutation are at higher risk for metastatic disease and disease-specific mortality. Gimenez-Togueplo and colleagues reported a rate of 87% (7 out of 8) malignancy rate with *SDHB* compared with a rate of 26% (20 out of 76) in non-*SDHB* PPGLs.⁶³ In a larger study by Neumann and colleagues, the rate of malignancy was 34.3% (11 out of 34) for patients with *SDHB*.⁶⁴ Disease-specific survival is also reduced when comparing patients with *SDHB* mutations and non-*SDHB* mutations. Amar and colleagues reported the 5-year survival after the diagnosis of metastases was 36% for those with *SDHB* mutation compared with 67% for those without *SDHB* mutations. The risk of death was 2.7 times higher by multivariate analysis in patients with *SDHB* mutation.⁶⁵ Therefore, these patients require biochemical testing as well as imaging to detect metastatic and/or early recurrence in the hopes that earlier detection can lead to improved treatment and survival.

PATHOLOGIC FEATURES

Malignant PPGLs are defined by the presence of chromaffin cells in tissues and sites that normally do not contain these cells. To predict their clinical behavior, Thompson and colleagues reported 100 patients with PPGLs. Half of the patients were deemed benign, while the other half was defined as malignant by histology with or without the presence of metastases. A histologically weighted pheochromocytoma of the adrenal gland scaled score (PASS) that assessed 12 histological factors was created. A PASS score ≥ 4 identified all tumors that were biologically aggressive.⁶⁶ Strong and colleagues validated the PASS score in a comparison of 43 patients with benign tumors and 5 patients with malignant tumors with a median follow-up of 43 months (range 6.7–220.6 months). Tumor necrosis, tumor cell spindling, and higher mitotic rate were the significant factors that differentiated malignant from benign behavior. A PASS score < 4 predicted benign pheochromocytomas, and therefore the authors recommended for close surveillance of any patients with a PASS score ≥ 4 .⁶⁷ However, the largest impediment to wide adoption of the PASS score relates to the inter- and intra-observer variation and scoring. Wu and colleagues assessed scoring by five experienced endocrine pathologists and found the scores to be widely variable. Therefore, the PASS score is not recommended for clinical prognostication at this time.⁶⁸

SURVEILLANCE

Current consensus guidelines recommend surveillance for the detection of recurrent disease postsurgical resection.^{19,69,70} However, the true incidence of recurrence as well as the optimal frequency, methods, and duration of follow-up are not well defined. In a systematic review and metaanalysis, Amar and colleagues⁷¹ evaluated the occurrence of “new events”

following resection PPGLs. A pooled incidence of 0.98 events/100 person-years (95% CI 0.71, 1.25) was calculated, which corresponds to an estimated 5 events per 100 patients followed-up for 5 years. Across the studies analyzed, paraganglioma (PGL) and familial disease were independent predictors of a higher risk of recurrence. An analysis of 701 patients from the European Network for the Study of Adrenal Tumors database, found that the overall risk of recurrences (local recurrence, distant metastases, and new tumors) was 10% within 5 years of follow-up.⁷⁰ In this study, PGL (versus pheochromocytoma), age < 20 years, hereditary disease, and tumor size > 15 cm were each associated with a recurrence risk of > 15%. In addition, patients with PGL and hereditary syndromes have the risk of late disease relapse (> 5 years).⁷⁰

Following resection for localized PPGL, early postoperative history, physical, and biochemical evaluation will establish completeness of resection and provide a postoperative baseline. Postoperative biochemical evaluation is ideally performed using the same sampling conditions and methods used preoperatively.^{19,70,72} Frequency and duration of subsequent surveillance are best assessed using an individualized approach that considers concern for persistent disease, history of tumor spillage, age and genetic status of the patient, and location and size of the primary tumor. Although a risk-stratified algorithm for surveillance is not available, a personalized approach should be utilized^{19,70}; For instance, in a 60-year-old patient with a small isolated sporadic PHEO, one may consider annual history and physical with biochemical evaluation for up to 10 years. However, a 20-year-old with an *SDHB* mutation and a history of resected multifocal PGL is best served with lifelong surveillance. Imaging should generally be reserved for symptomatic patients and positive screening laboratory values. Imaging may be required for surveillance in the rare patient with a biochemically inactive PPGL or in a patient who did not have any preoperative biochemical evaluation.

MANAGEMENT OF ADVANCED DISEASE

PPGLs are considered malignant when there is direct invasion into adjacent organs or when chromaffin tissue is present in areas normally lacking chromaffin cells. Common sites of distant metastases include liver, lung, bone, and lymph nodes. The treatment options for advanced disease are limited and include ¹³¹I MIBG, peptide receptor radionuclide therapy (PRRT), surgical debulking/cytoreduction, chemotherapy, and targeted therapies.

131I-MIBG

Since 1983, specialized centers around the world have used ¹³¹I-MIBG to treat patients with metastatic PPGLs. In a metaanalysis of 116 patients, Loh and colleagues⁷³ found that 76% of patients had symptomatic improvement, 30% of patients had tumor responses, and 45% of patients had a biochemical response with ¹³¹I-MIBG treatment. Gonias and colleagues evaluated high-dose ¹³¹I-MIBG treatment in 49 patients with metastatic PPGLs and found the overall response rate to be 22%. The estimated 5-year survival was 64% with a median follow-up time of 2 years (0.1–15 years).⁷⁴ The optimal dosing and the selection of patients who can benefit continue to be active areas of research.

PEPTIDE RECEPTOR RADIONUCLIDE THERAPY

Peptide receptor radionuclide therapy (PRRT) is an emerging therapy utilizing radiolabeled somatostatin analogues to treat metastatic neuroendocrine tumors, including PPGLs. In a series of 22 patients with metastatic PPGL and either disease progression and/or failure to control symptoms of catecholamine excess, Nastos and colleagues reviewed outcomes for patients allocated to either 123I-MIBG, 90Y-DOTATATE, or 177Lu-DOTATATE treatment based on MIBG or DOTATATE uptake. Although an improvement in progression-free survival was observed, two patients had received a combination of 123I-MIBG treatment and PRRT, rendering it difficult to conclude the superior modality. Identifying the optimal radionuclide analogue for progressive metastatic PPGLs is an active area of research.⁷⁵ The National Institutes of Health is currently enrolling and treating patients with progressive inoperable metastatic PPGLs with PRRT (NCT03206060) (Fig. 3).

SURGICAL DEBULKING/CYTOREDUCTION

The role of surgical debulking and cytoreduction of malignant PPGLs is not well defined. In a review of 30 patients who underwent surgical resection for metastatic PPGL, Ellis and colleagues found that complete resection of all gross disease (R0/R1) was critical to achieving a durable biochemical response and pharmacologic independence.⁷⁶ In contrast, R2 resection was almost invariably associated with either no response or partial response, and very few patients were able to discontinue alpha blockade for any meaningful period of time. Resection of metastatic PPGL should be reserved for patients in whom complete resection is anticipated or in situations where surgical debulking and cytoreduction will remove all the gross disease. However, selected patients who require surgical palliation may benefit and must be based on expert clinical and multidisciplinary judgement.

CHEMOTHERAPY AND TARGETED THERAPIES

Combination chemotherapy with cyclophosphamide, vincristine, and dacarbazine (CVD) has been the standard chemotherapy regimen for patients with malignant PPGLs. Averbuch and colleagues initial report in 1988 was a nonrandomized single-arm trial showing a complete and partial response rate of 57% (median duration of 21 months) and a complete and partial biochemical response rate of 79% (median duration greater than 22 months) in 14 patients with malignant PPGLs.⁷⁷ Tanabe and colleagues reported a nonrandomized single-arm trial of 17 patients with metastatic PPGL treated with CVD ($n = 17$). In this study, nearly 50% of patients responded to treatment, defined as either complete or partial biochemical response and/or partial tumor response (no patients in this study had complete tumor regression). The patients who responded to treatment had improvements in hypertension and impaired glucose tolerance. Moreover, the median survival was 6 years for responders, 4 years for nonresponders, and 3 years for those with progressive disease (median follow-up of 60 months, range 12–192 months).⁷⁸

Given the limited options of effective cytotoxic therapy for advanced PPGL, there is interest in molecular target therapies. In a small series of patients with progressive metastatic PPGL, Ayala-Ramirez and colleagues reported modest benefit with the multiple tyrosine

kinase receptor inhibitor, sunitinib. In this study, 8 of 14 patients with metastatic PPGLs and hypertension became normotensive, with 2 of those 8 patients discontinuing all antihypertensives. Despite promising results, the progression-free survival was only 4.1 months, indicating that better treatments are needed.⁷⁹ Further prospective multiinstitutional studies are needed to identify and define the best treatment for patients with malignant PPGLs.

CONCLUSIONS

Expert and experienced surgeons, endocrinologists, and anesthesiologists are required for the preoperative blood pressure and intravascular management of patients with PPGLs. After resection, patients with PPGLs have reasonable outcomes with an improved biochemical response and blood pressure control. Cortical-sparing adrenalectomy is the ideal approach for patients with germline mutations such as *VHL* and *RET*, whose adrenal tumors have a low malignancy potential to prevent steroid dependency. Pathological features of PPGLs have not been clearly delineated and will require further study. All patients with PPGLs require biochemical and potentially radiological surveillance. Advanced disease continues to be difficult to manage and is an important area of research.

ACKNOWLEDGMENT

This manuscript was reviewed by the SSO Endocrine and Head and Neck Disease Site Working Group, and all members expressed support for its publication.

DISCLOSURES

Dr. Yang's research is supported by the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health (K08HL145139).

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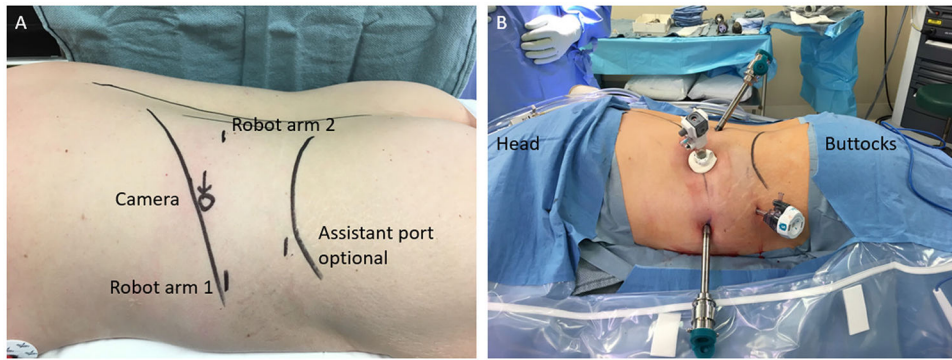


FIG. 1.
a Diagram outlining port placement for robotic retroperitoneoscopic approach to an adrenalectomy. **b** Patient prepped, draped, and ports placed for robotic retroperitoneal total adrenalectomy

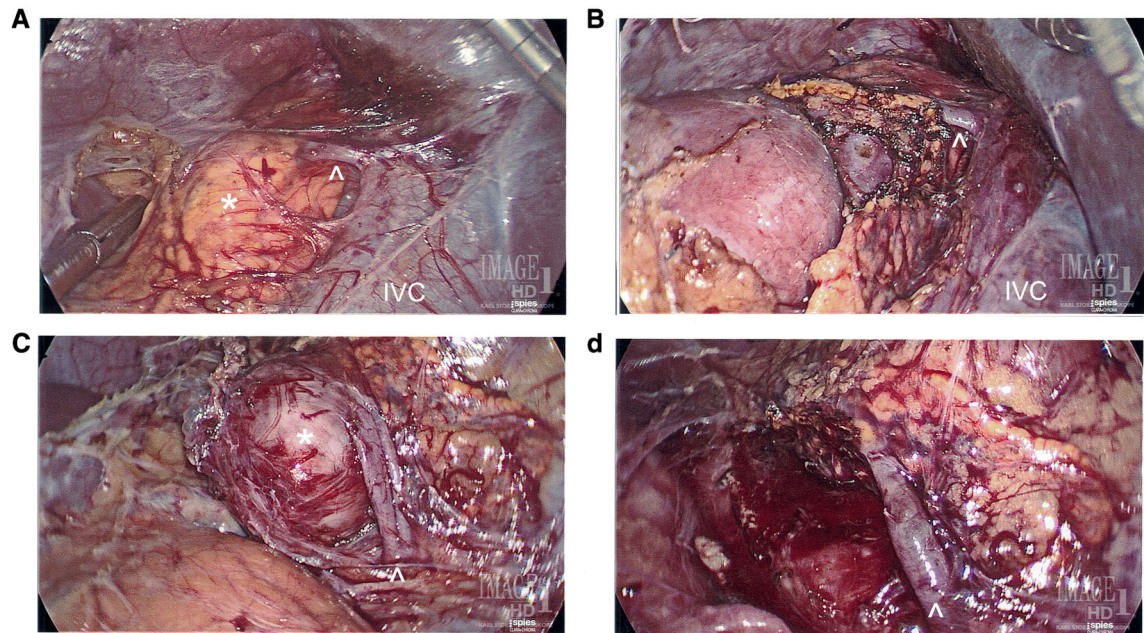


FIG. 2. Eleven-year-old male with VHL syndrome who underwent laparoscopic bilateral partial adrenalectomies guided with intraoperative ultrasound for bilateral pheochromocytomas. **a** Right adrenal tumor measuring 1.8 cm. **b** Post right partial adrenalectomy with preservation of the right adrenal vein. **c** Left adrenal tumor measuring 3.0 cm. **d** Post left partial adrenalectomy with preservation of the left adrenal vein. *Left and right adrenal tumors, respectively, ^Left and right adrenal veins, respectively, *IVC* inferior vena cava

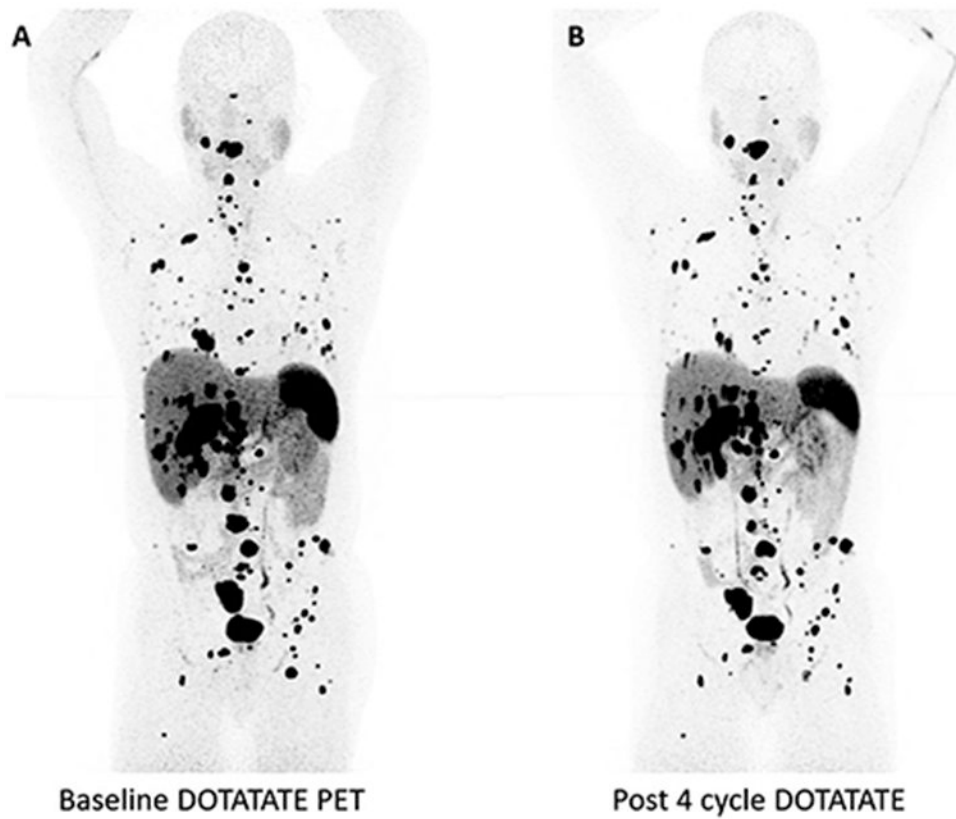


FIG. 3. A 59-year-old male with SDHB who underwent PRRT for progressive metastatic PPGL showing mild response after four cycles of treatment. **a** Baseline 68-gallium DOTATATE PET/CT scan showing widely metastatic disease. **b** 68-Gallium DOTATATE PET/CT scan showing mild tumor response after four cycles of Lutathera therapy

Medications used in preoperative management of pheochromocytoma and paraganglioma

TABLE 1

Drug	Class	Starting dose	Final dose	Side effects
Phenoxybenzamine ^a	Alpha-blocker	10 mg bid	1 mg/kg/day	Tachycardia, postural hypotension, nasal congestion, miosis, inhibition of ejaculation
Doxazosin ^a	Alpha-blocker	2 mg/day	32 mg/day	Dizziness, fatigue, somnolence, edema, dyspnea, hypotension, dry mouth
Propranolol	Beta-blocker	20 mg tid	40 mg tid	Fatigue, nausea, drowsiness, diarrhea, bronchitis, bradycardia, impotence, dry eyes
Atenolol	Beta-blocker	25 mg/day	50 mg/day	Fatigue, nausea, dizziness, bradycardia, postural hypotension, vertigo
Nifedipine	Calcium channel blocker	30 mg/day	60 mg/day	Dizziness, flushing, headache, weakness, nausea, muscle cramps, peripheral edema, anxiety, palpitation, dyspnea, nasal congestion
Amlodipine	Calcium channel blocker	5 mg/day	10 mg/day	Edema, dizziness, flushing, palpitation, fatigue, nausea, abdominal pain, somnolence
Metyrosine	Tyrosine hydroxylase inhibitor	250 mg/qid	4 g/day	Sedation, diarrhea, extrapyramidal signs such as drooling, speech difficulty, and tremor; anxiety, depression, confusion

^a Alpha blockade should start 7-14 days prior to surgery. Beta blockade should be initiated 3-4 days after alpha-blockade when necessary. Calcium channel blockers should be added as needed post alpha and beta blockade. Metyrosine should be offered as a fourth-line agent for patients who are refractory to alpha and calcium channel blockade

Excerpts from the Endocrine Society Guidelines for surgical management of pheochromocytomas and paragangliomas

TABLE 2

Surgical approaches

Minimally invasive adrenalectomy for most adrenal pheochromocytomas (recommendation; low-quality evidence)

Open resection for large (> 6 cm) or invasive pheochromocytomas (recommendation; very low-quality evidence)

Open resection for paragangliomas, with laparoscopic resection for small, noninvasive paragangliomas in surgically favorable locations (suggestion; very low-quality evidence)

Extent of adrenalectomy

Partial adrenalectomy for selected patients, such as those with hereditary pheochromocytoma, with small tumors who have already undergone a contralateral complete adrenalectomy to spare adrenal cortex and prevent permanent hypocortisolism (suggestion; very low-quality evidence)

Postoperative management

Postoperatively patients should have monitoring of blood pressure, heart rate and blood glucose levels with adjustment of associated therapies (strong recommendation; low-quality evidence)¹⁹
