



Published in final edited form as:

Clin Endocrinol (Oxf). 2016 July ; 85(1): 62–69. doi:10.1111/cen.13066.

Are patients with hormonally functional pheochromocytoma and paraganglioma initially receiving a proper adrenoceptor blockade? A retrospective cohort study

Henrique Vara Luiz, MD^{1,2}, Mary Jane Tanchee, MD^{1,3}, Maria G. Pavlatou, MD⁴, Run Yu, MD, PhD⁵, Joan Nambuba, BS¹, Katherine Wolf, BS¹, Tamara Prodanov, MD¹, Robert Wesley, PhD⁶, Karen Adams, MSc, CRNP¹, Tito Fojo, MD, PhD⁷, and Karel Pacak, MD, PhD, DSc¹

¹Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, Room 1E-3140, 10 Center Drive, Bethesda, MD 20892

²Department of Endocrinology and Diabetology, Hospital Garcia de Orta, Avenida Torrado da Silva, 2801-951 Almada, Portugal

³Section of Endocrinology and Metabolism, University of Santo Tomas Hospital, España, Manila, Philippines

⁴Clinical Neuroendocrinology Branch, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892

⁵Division of Endocrinology and Carcinoid and Neuroendocrine Tumor Center, Cedars-Sinai Medical Center, B-131, 8700 Beverly Blvd, Los Angeles, CA 90048

⁶Warren Grant Magnuson Clinical Center, National Institutes of Health, Building 10, Room 228, 10 Center Drive, Bethesda, MD 20892

⁷Center for Cancer Research, National Cancer Institute, National Institutes of Health, Building 10, Room 12C-103, 10 Center Drive, Bethesda, MD 20892

Abstract

Objective—Pharmacological treatment is mandatory in patients with hormonally functional pheochromocytoma and paraganglioma (PHAEO/PGL). We evaluated if patients initially diagnosed with hormonally functional PHAEO/PGL by various medical subspecialties received proper adrenoceptor blockade, and analyzed factors predicting the prescription of adequate treatment.

Methods—In a retrospective cohort study we reviewed data from patients initially diagnosed with hormonally functional PHAEO/PGL outside the National Institutes of Health and Cedars-

Corresponding Author: Karel Pacak, MD, PhD, DSc, Chief, Section on Medical Neuroendocrinology, Professor of Medicine, Program in Reproductive and Adult Endocrinology, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Building 10, CRC, Room 1E-3140, 10 Center Drive MSC-1109, Bethesda, MD 20892, Phone: (301) 402-4594, Fax: (301) 402-4712, karel@mail.nih.gov.

Conflict of Interest: None.

Sinai Medical Center, who were referred to these institutions between January 2001 and April 2015. Logistic regression was used to assess factors associated with proper adrenoceptor blockade.

Results—A total of 381 patients were included. Adequate pharmacological treatment was prescribed to 69.3%, of which 93.1% received α -adrenoceptor blockers. Regarding patients who were inappropriately treated, 53% did not receive any medication. Independent predictors of the prescription of a proper blockade were the diagnosis by endocrinologists (odds ratio [OR] 4.14; 95% confidence interval [CI], 2.51–6.85; $p < 0.001$), the presence of high blood pressure (OR 5.94; 95% CI, 3.11–11.33; $p < 0.001$) and the evidence of metastasis (OR 5.96; 95% CI, 1.93–18.46; $p = 0.002$).

Conclusions—Although most patients received adequate pharmacological treatment, almost one-third were either not treated or received inappropriate medications. The diagnosis by endocrinologists, the presence of high blood pressure and the evidence of metastatic disease were identified as independent predictors of a proper blockade. These results highlight the need to educate physicians about the importance of starting adequate adrenoceptor blockade in all patients with hormonally functional PHAEO/PGL.

Keywords

phaeochromocytoma; paraganglioma; hormonally functional; adrenoceptor blockade; medical subspecialties

INTRODUCTION

Phaeochromocytoma and paraganglioma (PHAEO/PGL) are rare neuroendocrine tumours, with an estimated prevalence of 1:6500 to 1:2500, and an annual incidence of 1.5 to 9 cases per million people.^{1,2} While PHAEOs are defined as tumours arising from catecholamine-producing chromaffin cells in the adrenal medulla, closely related lesions of extra-adrenal sympathetic and parasympathetic paraganglia are known as PGLs.³ PHAEOs and sympathetic PGLs almost always secrete catecholamines, whereas parasympathetic PGLs, located mainly in the head and neck, are usually biochemically silent.¹ The main signs and symptoms are related to episodic or permanent catecholamine release and include hypertension, palpitations, headaches, sweating and pallor. Episodic catecholamine secretion is often unpredictable, although it may occur if the tumour is manipulated or stimulated (e.g. during physical examination, anaesthesia, physical or psychological stress, etc.). This may result in severe, often life-threatening, complications such as hypertensive crisis, myocardial infarction, arrhythmia, stroke or organ ischaemia.^{1,2,4–6}

It is mandatory to suspect, diagnose and treat PHAEO/PGL. Proper pharmacological treatment, usually referred to as adrenoceptor blockade, is required to control the clinical features and reduce cardiovascular and other organ risks by blocking the effects of released catecholamines. It should be started immediately after the diagnosis of a hormonally functional PHAEO/PGL (defined as catecholamine-producing) and, if surgery is planned, the drugs should be introduced at least 7 to 14 days before the procedure.^{1,4,7,8} Randomized controlled clinical studies comparing the effectiveness of available therapeutic options are missing. However, several authors have reviewed this topic and shared their clinical

experience in using different drugs for treatment as well as for preoperative preparation of patients with PHAEO/PGL.^{1,4,8-16} Nevertheless, the previous and recent guidelines of the United States (US) Endocrine Society formulated evidence-based recommendations about the perioperative management of patients with catecholamine-producing PHAEO/PGL.^{7,17} Thus, α -adrenoceptor blockers are suggested as the first-line drug, including the nonselective α -adrenoceptor blocker phenoxybenzamine and the α_1 -selective antagonists namely doxazosin, terazosin and prazosin.¹⁸⁻²⁰ Calcium channel blockers (CCBs) such as amlodipine, nicardipine, nifedipine and verapamil are considered alternative drugs, especially for normotensive or mildly hypertensive patients as well as for those who develop severe adverse effects with α -adrenoceptor blockers.²¹⁻²³ If hypertension persists, combined medications can be used. β -Adrenoceptor blockers, either nonselective (e.g. propranolol) or β_1 -selective (e.g. atenolol and metoprolol), are recommended to be added to control tachycardia, but they should never be prescribed before the introduction of an α -adrenoceptor blocker due to the risk of triggering a hypertensive crisis.^{24,25} Combined α - and β -adrenoceptor blockers such as labetalol and carvedilol are not indicated as first-line drugs given their more potent β -antagonistic activity.^{26,27} α -Methyl- ρ -tyrosine (metyrosine), a catecholamine synthesis inhibitor, is also recommended as an add-on drug.^{28,29} Pharmacological treatment in children is similar to that performed in adults.^{30,31} The same recommendations have been in place for many years, particularly during the period of data collection of the present study (last 15 years).

Our long-standing clinical experience at the National Institutes of Health (NIH) and Cedars-Sinai Medical Center suggests that a significant number of patients with PHAEO/PGL do not receive adequate adrenoceptor blockade, although most of these patients present with hormonally functional PHAEO/PGL and have hypertension and/or tachycardia. Therefore, the main aim of the present study was to carefully evaluate if individuals initially diagnosed with hormonally functional PHAEO/PGL were appropriately blocked and to identify factors associated with proper pharmacological treatment or with an inadequate prescription.

MATERIALS AND METHODS

Study design and Patients

A retrospective cohort analysis was performed. Our cohort comprised patients diagnosed with PHAEO/PGL outside the NIH and Cedars-Sinai Medical Center, who were referred to these institutions for further evaluation or treatment between January 2001 and April 2015. Patients were referred from different medical facilities and practices worldwide, but mostly from the US. All cases had confirmed PHAEO/PGL on histopathology. We excluded those with biochemically silent tumours (normal plasma and/or urinary catecholamine and metanephrine levels) and those without available plasma and/or urinary catecholamine and metanephrine measurements performed at the initial diagnosis of PHAEO/PGL. We only included patients with precise data about the first pharmacological treatment (or its absence) prescribed when the initial diagnosis of PHAEO/PGL was established, regardless of the decision to perform surgery or other interventions. Only patients who had accurate information regarding the medical subspecialty that made the first drug prescription were eligible for review. This study was approved by the Institutional Review Board (IRB) of the

Eunice Kennedy Shriver National Institute of Child Health and Human Development, NIH and by the IRB of the Cedars-Sinai Medical Center.

Primary outcome

The primary outcome was the prescription of an appropriate adrenoceptor blockade by the physician who initially diagnosed hormonally functional PHAEO/PGL and conveyed this information to the patient for the first time ever. We defined appropriate treatment as: 1) α -adrenoceptor blockers alone; 2) α -adrenoceptor blockers followed by β -adrenoceptor blockers; 3) α -adrenoceptor blockers with other anti-hypertensive drugs such as CCBs, metyrosine, angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs); 4) CCBs alone; and 5) CCBs with ACE inhibitors or ARBs. Inappropriate treatment included the following drug combinations: 1) β -adrenoceptor blockers and α -adrenoceptor blockers (both drugs given at the same time); 2) β -adrenoceptor blockers alone; 3) combined α - and β -adrenoceptor blockers; 4) β -adrenoceptor blockers given before the administration of other anti-hypertensive drugs; 5) ACE inhibitors alone; and 6) ARBs alone.

Covariates

Covariates were collected at the time of the initial PHAEO/PGL diagnosis and included the patient's gender, age, tumour location, identification of metastasis, evidence of signs and symptoms related to a catecholamine-producing tumour, presence of high blood pressure (BP), evidence of tachycardia and medical subspecialty that made the diagnosis and medically treated the patient.

Individuals were considered to be symptomatic if any of the following were present: hypertension, headache, palpitations, tachycardia, sweating, pallor, anxiety/nervousness, dizziness, nausea, vomiting, constipation, tremor, fatigue, weight changes, visual disturbances and chest or abdominal pain. Hypertension was characterized by a systolic BP higher than 140 mmHg and/or a diastolic BP higher than 90 mmHg in adult patients. In those under 18 years of age, it was defined as a systolic or diastolic BP greater than or equal to the 95th percentile for sex, age and height. Tachycardia was defined as a resting heart rate (HR) over 100 beats per minute in adult patients, whereas in children, a HR higher than the age-specific reference range was used to define tachycardia.

Statistical analysis

To identify predictive factors of appropriate pharmacological treatment, we first performed a univariate analysis using Fisher's exact test. Statistically significant variables were studied by a forward stepwise logistic regression (multivariate) to assess which factors contributed most directly to the model. Numeric variables were summarized as the mean \pm standard deviation. Odds ratio (OR) and 95% confidence interval (CI) were used to report the results of logistic regression analysis. A 2-sided p value less than 0.05 was considered statistically significant. Analysis was performed using IBM SPSS Statistics for Windows, version 21.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Characteristics of patients at diagnosis

We analyzed data from 488 patients who were first diagnosed with PHAEO/PGL outside the NIH and Cedars-Sinai Medical Center and were later referred to either of the two institutions for further evaluation or treatment during the last 15 years. Of these patients, 107 were excluded due to the following reasons: biochemically silent tumours (n = 28), no available plasma and/or urinary catecholamine and metanephrine measurements (n = 37), insufficient data about the pharmacological treatment prescribed when the initial diagnosis of PHAEO/PGL was made and the information was given to the patient for the first time (n = 26), and subspecialty not identified (n = 16).

Thus, a total of 381 patients with hormonally functional PHAEO/PGL were included in the study, corresponding to 196 males (51.4%) and 185 females (48.6%). Mean age at diagnosis was 37.9 ± 17.5 years and most patients were adults (85.6%). The most common tumour location was adrenal PHAEO (64.6%) followed by abdominal and pelvic PGL (26.2%). The majority of patients presented with solitary lesions (79.8%), while multiple tumours and metastatic disease were identified at diagnosis in 11% and 9.2% of cases, respectively. Regarding biochemical data, most patients had both elevated catecholamine and metanephrine levels (79.8%), whereas 15.2% presented only with high metanephrines (metanephrine and/or normetanephrine) and 5% had increased catecholamines alone (epinephrine, norepinephrine and/or dopamine). Normetanephrine and metanephrine levels were elevated in 92.1% and 45.1% of patients, respectively. High norepinephrine values were found in 78% of cases, whereas the levels of epinephrine and dopamine were elevated in 28.3% and 12.9%, respectively. At least 92.7% of patients presented with clinical features related to a catecholamine-producing tumour. Hypertension was identified in 80.6%, while tachycardia was found in 49.6% of cases. More than half of the patients were diagnosed by endocrinologists (59.3%); the remaining individuals were first managed by a number of other subspecialties (Table 1).

Pharmacological treatment prescribed when the initial diagnosis of hormonally functional PHAEO/PGL was established

Of the 381 patients, adequate pharmacological treatment was prescribed to 264 (69.3%). Of these cases, the majority received α -adrenoceptor blockers (93.1%): alone (56.4%), followed by β -adrenoceptor blockers (29.5%) or in combination with other anti-hypertensive drugs (7.2%). CCBs were given to 6.9% of appropriately treated patients. Overall, 117 (30.7%) were not properly treated. Most of them did not receive any drug (53%), whereas 12% were given β -adrenoceptor blockers and α -adrenoceptor blockers at the same time, 9.4% received β -adrenoceptor blockers alone and 7.7% were treated with combined α - and β -adrenoceptor blockers; the remaining patients received β -adrenoceptor blockers in combination with other anti-hypertensive drugs and ACE inhibitors or ARBs alone (Table 2).

Regarding the drugs used for the initial treatment either alone or in combination (Table 3), phenoxybenzamine was the preferred α -adrenoceptor blocker (61.9%), followed by doxazosin (10.4%). The type of α -adrenoceptor blocker was unknown in 18.1% of cases.

The most common β -adrenoceptor blocker was metoprolol (41.4%), followed by atenolol (16.2%), whereas this information was not available in 27.9% of cases. Labetalol was the drug of choice in 77.8% of patients treated with combined α - and β -adrenoceptor blockers. Amlodipine was identified as the preferred CCB (61.3%).

Predictors of the prescription of adequate pharmacological treatment

In the univariate analysis, we found that the probability of appropriate adrenoceptor blockade was higher for patients presenting with a PHAEO than for those with a PGL (73.6 vs. 60.6%; $p = 0.013$), for those with metastatic vs. non-metastatic disease (85.7 vs. 67.6%; $p = 0.033$), for those with signs and symptoms vs. asymptomatic cases despite positive biochemistry (70% vs. 41.2%; $p = 0.017$) and for hypertensive patients when compared to those with normal BP, again despite positive biochemistry (74.3% vs. 48.6%; $p < 0.001$). In addition, patients diagnosed by endocrinologists were more likely to be properly treated than those managed by other medical subspecialties (81% vs. 52.3%; $p < 0.001$). In the multivariate analysis using forward stepwise logistic regression, the best predictor of the prescription of adequate blockade was the management by endocrinologists (OR 4.14; 95% CI, 2.51–6.85; $p < 0.001$), followed by the presence of high BP (OR 5.94; 95% CI, 3.11–11.33; $p < 0.001$), followed by the evidence of metastatic disease (OR 5.96; 95% CI, 1.93–18.46; $p = 0.002$). The remaining factors did not add significance when these three variables were in the model (Table 4). Although most subspecialties were found to have a lower rate of properly treated patients when compared to endocrinologists, nephrologists and paediatricians had proportions of appropriate blockade (88.9% and 78.6%, respectively) comparable to endocrinologists (Table 5). Furthermore, of patients who were inappropriately blocked, 91.4% presented at diagnosis with at least one sign or symptom related to catecholamine excess, 67.5% had high BP, 48.7% had tachycardia and 80.3% presented with either high BP or tachycardia, or both.

Interestingly, among patients diagnosed by endocrinologists (Table 6), adequate pharmacological treatment was prescribed to 85.4% of those with high BP versus 61% of those with normal BP ($p = 0.001$). All individuals with metastatic disease received appropriate blockade compared to 79.2% of those without metastasis ($p = 0.028$). On the other hand, regarding patients managed by other subspecialties, we found that proper adrenoceptor blockade was given to 57.4% of those with high BP vs. 33.3% of those with normal BP ($p = 0.018$) and to 68.8% of patients with metastasis vs. 50.4% of those without metastasis ($p = 0.194$).

DISCUSSION

According to many reports, including the US Endocrine Society guidelines, all patients with hormonally functional PHAEO/PGL should receive proper adrenoceptor blockade.⁷ The blockade should be started immediately after the initial diagnosis of hormonally functional PHAEO/PGL is established. Such treatment is crucial to block the action of released catecholamines, therefore preventing severe cardiovascular and other organ-specific complications. Our study is the first to focus on the adequacy of pharmacological treatment prescribed by various medical subspecialties at the time of initial diagnosis of hormonally

functional PHAEO/PGL, regardless of the decision to perform surgery or other procedures including chemo- or radiotherapy. In addition, we included a very large population of 381 individuals.

The present study shows that more than two-thirds of individuals received adequate pharmacological treatment when the initial diagnosis of PHAEO/PGL was performed. The vast majority of these patients received α -adrenoceptor blockers: alone, followed by β -adrenoceptor blockers or in combination with other anti-hypertensive drugs such as CCBs, metyrosine, ACE inhibitors and ARBs. This is in agreement with the US Endocrine Society guidelines.⁷ In addition, a minority of appropriately treated patients received CCBs, which are also allowed by these guidelines. Endocrinologists had higher rates of adequate treatment when compared to other subspecialties. However, the primary outcome for nephrologists and paediatricians was similar to that of endocrinologists, although they treated a much smaller number of patients. Proper adrenoceptor blockade was also significantly influenced by the presence of high BP and by the evidence of metastatic disease at diagnosis.

Nevertheless, the results of the present study indicate that about one-third of patients with hormonally functional PHAEO/PGL were not properly treated. These individuals were more likely to be managed by several other medical subspecialties such as family medicine, surgery, internal medicine, cardiology and oncology. Inappropriate pharmacological treatment was mainly associated with the presence of normal BP and the absence of metastasis when the diagnosis of PHAEO/PGL was made. Thus, more than half of normotensive cases and about one-third of patients without evidence of metastasis did not receive adequate blockade despite all of these patients having evidence of catecholamine excess. Furthermore, a significant proportion of inappropriately blocked patients presented at diagnosis with signs and symptoms related to catecholamine excess (91.4%), namely high BP (67.5%) and tachycardia (48.7%). Despite the overall better outcome provided by endocrinologists, patients with normal BP and those without metastatic disease were less likely to be properly treated by these physicians as well.

One worrisome observation from our study is that more than half of inappropriately blocked patients did not receive any pharmacological blockade. Therefore, they could be at risk of severe cardiovascular and other organ-related complications due to catecholamine excess, as previously reviewed.^{4,15} Another alarming finding was that β -adrenoceptor blockers (alone, in combination with other anti-hypertensive drugs or as combined α - and β -adrenoceptor blockers) were given as initial therapy to 11% of all patients. As numerous published, this could result in a hypertensive crisis in the absence of previous administration of α -adrenoceptor blockers.^{24,27} This is always an important teaching point in medical school and during postgraduate education, often appearing as a board question for endocrinologists. Data regarding clinical outcome and evidence of complications is not available since the present study solely focused on the prescription of pharmacological treatment when the initial diagnosis of PHAEO/PGL was established.

Physicians from various subspecialties should be aware that adrenoceptor blockade is mandatory for patients with hormonally functional PHAEO/PGL, regardless of the presence

of clinical features related to catecholamine excess or metastatic disease. Patients with hormonally functional PHAEO/PGL despite presenting with normal BP may unpredictably become hypertensive (especially when the tumour is manipulated or under severe stress conditions) and they should also receive pharmacological treatment with α -adrenoceptor blockers or rarely CCBs.^{4,7,32,33} The only exceptions where blockade may not be required are patients with parasympathetic-derived head and neck PGLs that do not produce catecholamines or those with tumours producing only dopamine.⁹ According to our best knowledge and experience, if a tumour secretes only dopamine, adrenoceptor blockade is not necessary because dopamine and methoxytyramine do not cause any serious cardiovascular events either before or during surgery. Nowadays, the evaluation and identification of hormonally functional PHAEO/PGL is better performed by measuring plasma or urinary metanephrines and recently by methoxytyramine.^{34,35} The question regarding the prescription of pharmacological blockade in patients with biochemically silent PHAEO/PGL is still unresolved and it should be evaluated by properly conducted prospective studies, namely by several independent medical centres.

The results of the present study also suggest that patients with PHAEO/PGL should be referred to endocrinologists when the initial diagnosis is established, given the higher rate of adequate pharmacological treatment provided by this medical subspecialty. In addition, management by a multidisciplinary team consisting of endocrinologists, anaesthetists, surgeons, cardiologists, oncologists, radiologists, nuclear medicine physicians, paediatricians and internists is also mandatory in order to provide excellent care and therapeutic plans for these patients and to reduce the morbidity and mortality related to PHAEO/PGL.^{4,8,9}

Our study has important limitations. First, due to its retrospective design, information about the prescribed adrenoceptor blockade was sometimes limited to its pharmacological class. Additionally, some discrepancies between the reported and the prescribed medication may need to be considered. However, we have made the best effort to avoid such errors including double checking the prescription and in some cases clarifying it by calling the physicians and patients. Second, some factors that may affect the therapeutic decision including patient preferences could not be ascertained. Third, most patients were diagnosed by endocrinologists whereas other subspecialties managed a limited number of cases, making it impossible to compare the outcomes of each subspecialty. Fourth, there are other factors that could possibly be associated with the prescription of appropriate blockade, such as the clinical experience of physicians of various medical subspecialties in treating individuals with PHAEO/PGL. Additionally, some referring physicians may have felt that certain patients (e.g. normotensive with only mildly elevated catecholamine/metanephrine levels) could wait a short period of time without pharmacological treatment until evaluation in a specialized centre, while others might not be comfortable in prescribing medical therapy and would choose to refer patients for advice. Fifth, we were not able to collect any meaningful data related to the measurement of methoxytyramine that is still not available in the US, except currently at the NIH. Therefore, these data were incomplete and unavailable for any statistical analysis in the present study. Finally, this study was not aimed to assess any clinical outcome related to the prescription of appropriate and inappropriate pharmacological treatment or to evaluate the doses and duration of the administered drugs.

CONCLUSION

In this large retrospective study, we found that although most patients received adequate pharmacological treatment after the diagnosis of PHAEO/PGL, almost one-third of cases were either not treated or received inappropriate medications. The diagnosis by endocrinologists, the presence of high BP and the evidence of metastatic disease were identified as the most important predictive factors for the prescription of a proper blockade. It is crucial to educate physicians of various medical subspecialties about the importance of starting adequate adrenoceptor blockade in all patients with hormonally functional PHAEO/PGL, including those presenting with normal BP and HR. Treatment should be introduced immediately after the initial diagnosis of PHAEO/PGL is established. Further research is needed to ascertain our findings in order to avoid life-threatening organ complications in patients with hormonally functional PHAEO/PGL and to evaluate the best approach for patients with only dopamine-producing or biochemically silent (but not necessarily catecholamine non-producing) PHAEO/PGL.

Acknowledgments

Funding: This study was supported by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health.

Abbreviations

ACE inhibitors	angiotensin-converting enzyme inhibitors
ARB	angiotensin II receptor blocker
BP	blood pressure
CCB	calcium channel blocker
CI	confidence interval
HR	heart rate
IRB	Institutional Review Board
metirosine	α -methyl- ρ -tyrosine
NIH	National Institutes of Health
OR	odds ratio
PGL	paraganglioma
PHAEO	phaeochromocytoma
PHAEO/PGL	phaeochromocytoma and paraganglioma
US	United States

References

1. Chen H, Sippel RS, O'Dorisio MS, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. *Pancreas*. 2010; 39:775–783. [PubMed: 20664475]
2. Joynt KE, Moslehi JJ, Baughman KL. Paragangliomas: etiology, presentation, and management. *Cardiology in Review*. 2009; 17:159–164. [PubMed: 19525677]
3. Lloyd, RV.; Tischler, AS.; Kimura, N., et al. Adrenal tumours: introduction. In: DeLellis, RA.; Lloyd, RV.; Heitz, PU.; Eng, C., editors. World Health Organization classification of tumours. Pathology and genetics of tumours of endocrine organs. IARC Press; Lyon: 2004. p. 137-138.
4. Pacak K. Preoperative management of the pheochromocytoma patient. *The Journal of Clinical Endocrinology and Metabolism*. 2007; 92:4069–4079. [PubMed: 17989126]
5. Luiz HV, da Silva TN, Pereira BD, et al. Malignant paraganglioma presenting with hemorrhagic stroke in a child. *Pediatrics*. 2013; 132:e1709–e1714. [PubMed: 24276837]
6. Brouwers FM, Eisenhofer G, Lenders JW, et al. Emergencies caused by pheochromocytoma, neuroblastoma, or ganglioneuroma. *Endocrinology and Metabolism Clinics of North America*. 2006; 35:699–724. [PubMed: 17127142]
7. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*. 2014; 99:1915–1942. [PubMed: 24893135]
8. Pacak, K.; Eisenhofer, G.; Ahlman, H., et al. Nature Clinical Practice Endocrinology & Metabolism; Pheochromocytoma: recommendations for clinical practice from the First International Symposium; October 2005; 2007. p. 92-102.
9. Mannelli M. Management and treatment of pheochromocytomas and paragangliomas. *Annals of the New York Academy Sciences*. 2006; 1073:405–416.
10. Mazza A, Armigliato M, Marzola MC, et al. Anti-hypertensive treatment in pheochromocytoma and paraganglioma: current management and therapeutic features. *Endocrine*. 2014; 45:469–478. [PubMed: 23817839]
11. Galati SJ, Said M, Gospin R, et al. The mount sinai clinical pathway for the management of pheochromocytoma. *Endocrine Practice*. 2015; 21:368–382. [PubMed: 25297659]
12. Chew SL. Recent developments in the therapy of pheochromocytoma. *Expert Opinion on Investigational Drugs*. 2004; 13:1579–1583. [PubMed: 15566315]
13. van der Horst-Schrivers AN, Kerstens MN, Wolffenbuttel BH. Preoperative pharmacological management of phaeochromocytoma. *The Netherlands Journal of Medicine*. 2006; 64:290–295. [PubMed: 16990692]
14. Lentschener C, Gaujoux S, Tesniere A, et al. Point of controversy: perioperative care of patients undergoing pheochromocytoma removal - time for a reappraisal? *European Journal of Endocrinology*. 2011; 165:365–373. [PubMed: 21646289]
15. Lenders JW, Eisenhofer G, Mannelli M, et al. Phaeochromocytoma. *Lancet*. 2005; 366:665–675. [PubMed: 16112304]
16. Young WF Jr. Pheochromocytoma: 1926–1993. *Trends in Endocrinology and Metabolism*. 1993; 4:122–127. [PubMed: 18407145]
17. Bravo EL, Tagle R. Pheochromocytoma: state-of-the-art and future prospects. *Endocrine Reviews*. 2003; 24:539–553. [PubMed: 12920154]
18. van der Zee PA, de Boer A. Pheochromocytoma: a review on preoperative treatment with phenoxybenzamine or doxazosin. *The Netherlands Journal of Medicine*. 2014; 72:190–201. [PubMed: 24829175]
19. Li J, Yang CH. Improvement of preoperative management in patients with adrenal pheochromocytoma. *International Journal of Clinical and Experimental Medicine*. 2014; 7:5541–5546. [PubMed: 25664068]
20. Agrawal R, Mishra SK, Bhatia E, et al. Prospective study to compare peri-operative hemodynamic alterations following preparation for pheochromocytoma surgery by phenoxybenzamine or prazosin. *World Journal of Surgery*. 2014; 38:716–723. [PubMed: 24233658]

21. Brunaud L, Boutami M, Nguyen-Thi PL, et al. Both preoperative alpha and calcium channel blockade impact intraoperative hemodynamic stability similarly in the management of pheochromocytoma. *Surgery*. 2014; 156:1410–1417. [PubMed: 25456922]
22. Lebuffe G, Dosseh ED, Tek G, et al. The effect of calcium channel blockers on outcome following the surgical treatment of pheochromocytomas and paragangliomas. *Anaesthesia*. 2005; 60:439–444. [PubMed: 15819762]
23. Siddiqi HK, Yang HY, Laird AM, et al. Utility of oral nicardipine and magnesium sulfate infusion during preparation and resection of pheochromocytomas. *Surgery*. 2012; 152:1027–1036. [PubMed: 23158177]
24. Sheaves R, Chew SL, Grossman AB. The dangers of unopposed beta-adrenergic blockade in pheochromocytoma. *Postgraduate Medical Journal*. 1995; 71:58–59. [PubMed: 7708599]
25. Sibal L, Jovanovic A, Agarwal SC, et al. Pheochromocytomas presenting as acute crises after beta blockade therapy. *Clinical Endocrinology*. 2006; 65:186–190. [PubMed: 16886958]
26. Reach G, Thibonnier M, Chevillard C, et al. Effect of labetalol on blood pressure and plasma catecholamine concentrations in patients with pheochromocytoma. *British Medical Journal*. 1980; 280:1300–1301. [PubMed: 7388518]
27. Briggs RS, Birtwell AJ, Pohl JE. Hypertensive response to labetalol in pheochromocytoma. *Lancet*. 1978; 1:1045–1046. [PubMed: 76965]
28. Steinsapir J, Carr AA, Prisant LM, et al. Metyrosine and pheochromocytoma. *Archives of Internal Medicine*. 1997; 157:901–906. [PubMed: 9129550]
29. Perry RR, Keiser HR, Norton JA, et al. Surgical management of pheochromocytoma with the use of metyrosine. *Annals of Surgery*. 1990; 212:621–628. [PubMed: 1978640]
30. Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. *The Journal of Clinical Endocrinology and Metabolism*. 2010; 95:2023–2037. [PubMed: 20215394]
31. Havekes B, Romijn JA, Eisenhofer G, et al. Update on pediatric pheochromocytoma. *Pediatric Nephrology*. 2009; 24:943–950. [PubMed: 18566838]
32. Agarwal A, Gupta S, Mishra AK, et al. Normotensive pheochromocytoma: institutional experience. *World Journal of Surgery*. 2005; 29:1185–1188. [PubMed: 16091986]
33. Shen SJ, Cheng HM, Chiu AW, et al. Perioperative hypertensive crisis in clinically silent pheochromocytomas: report of four cases. *Chang Gung Medical Journal*. 2005; 28:44–50. [PubMed: 15804148]
34. Eisenhofer G, Goldstein DS, Sullivan P, et al. Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. *The Journal of Clinical Endocrinology and Metabolism*. 90:2068–2075. [PubMed: 15644397]
35. van Duinen N, Corssmit EP, de Jong WH, et al. Plasma levels of free metanephrines and 3-methoxytyramine indicate a higher number of biochemically active HNPGL than 24-h urinary excretion rates of catecholamines and metabolites. *European Journal of Endocrinology*. 2013; 169:377–382. [PubMed: 23832865]

Table 1

Characteristics of patients with hormonally functional PHAEO/PGL at diagnosis.

Patient characteristics	Patients (n = 381), n (%)
Gender	
Male	196 (51.4)
Female	185 (48.6)
Age	
< 18 y	55 (14.4)
18 y	326 (85.6)
Mean age (SD), y	37.9 (17.5)
Tumour location	
Adrenal PHAEO	246 (64.6)
Head and neck PGL	18 (4.7)
Chest PGL	8 (2.1)
Abdominal and pelvic PGL	100 (26.2)
PHAEO + head and neck PGL	3 (0.8)
PHAEO + abdominal PGL	5 (1.3)
Head and neck PGL + abdominal PGL	1 (0.3)
Number of tumours	
Solitary	304 (79.8)
Multiple	42 (11)
Metastatic	35 (9.2)
Positive biochemistry	
Metanephrines + catecholamines	304 (79.8)
Metanephrines	58 (15.2)
Catecholamines	19 (5)
Signs and symptoms	
Present	353 (92.7)
Absent	17 (4.5)
Unknown	11 (2.9)
Blood pressure	
High	307 (80.6)
Normal	74 (19.4)
Tachycardia	
Present	189 (49.6)
Absent	192 (50.4)
Medical subspecialty	
Endocrinology	226 (59.3)
Surgery	35 (9.2)
Internal medicine	24 (6.3)

Patient characteristics	Patients (n = 381), n (%)
Cardiology	21 (5.5)
Family medicine	18 (4.7)
Nephrology	18 (4.7)
Oncology	15 (3.9)
Paediatrics	14 (3.7)
Other	10 (2.6)

PGL = paraganglioma; PHAEO = phaeochromocytoma; SD = standard deviation.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 2

Type of pharmacological treatment prescribed after the initial diagnosis of hormonally functional PHAEO/PGL.

Type of treatment	Patients, n (%)
Appropriate treatment (n = 264)	
α -Adrenoceptor blockers alone	149 (56.4)
α -Adrenoceptor blockers followed by β -adrenoceptor blockers	78 (29.5)
α -Adrenoceptor blockers with CCBs	8 (3)
α -Adrenoceptor blockers with metyrosine	7 (2.7)
α -Adrenoceptor blockers with ACE inhibitors	3 (1.1)
α -Adrenoceptor blockers with ARBs	1 (0.4)
CCBs alone	16 (6.1)
CCBs with ACE inhibitors	1 (0.4)
CCBs with ARBs	1 (0.4)
Inappropriate treatment (n = 117)	
No treatment	62 (53)
β -Adrenoceptor blockers and α -adrenoceptor blockers at the same time	14 (12)
β -Adrenoceptor blockers alone	11 (9.4)
Combined α - and β -adrenoceptor blockers	9 (7.7)
β -Adrenoceptor blockers with CCBs	5 (4.3)
β -Adrenoceptor blockers with ACE inhibitors	1 (0.9)
β -Adrenoceptor blockers with ARBs	1 (0.9)
β -Adrenoceptor blockers with clonidine	1 (0.9)
ACE inhibitors alone	8 (6.8)
ARBs alone	5 (4.3)

ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CCBs = calcium channel blockers; metyrosine = α -methyl- p -tyrosine; PHAEO/PGL = pheochromocytoma and paraganglioma.

Table 3

Drugs used for the initial pharmacological treatment of patients with hormonally functional PHAEO/PGL either alone or in combination.

Drugs	Patients, n (%)
α-Adrenoceptor blockers (n = 260)	
Phenoxylbenzamine	161 (61.9)
Doxazosin	27 (10.4)
Prazosin	18 (6.9)
Terazosin	7 (2.7)
Unknown	47 (18.1)
β-Adrenoceptor blockers (n = 111)	
Metoprolol	46 (41.4)
Atenolol	18 (16.2)
Propranolol	12 (10.8)
Bisoprolol	3 (2.7)
Acebutolol	1 (0.9)
Unknown	31 (27.9)
Combined α- and β-adrenoceptor blockers (n = 9)	
Labetalol	7 (77.8)
Carvedilol	2 (22.2)
CCBs (n = 31)	
Amlodipine	19 (61.3)
Diltiazem	6 (19.4)
Verapamil	3 (9.7)
Nifedipine	2 (6.5)
Nicardipine	1 (3.2)
ACE inhibitors (n = 13)	
Lisinopril	12 (92.3)
Enalapril	1 (7.7)
ARBs (n = 8)	
Valsartan	4 (50)
Losartan	3 (37.5)
Unknown	1 (12.5)
Metyrosine (n = 7)	
Clonidine (n = 1)	

ACE inhibitors = angiotensin-converting enzyme inhibitors; ARBs = angiotensin II receptor blockers; CCBs = calcium channel blockers; metyrosine = α -methyl- p -tyrosine; PHAEO/PGL = pheochromocytoma and paraganglioma.

Association between the characteristics of patients with hormonally functional PHAEO/PGL and the prescription of a proper pharmacological treatment.

Table 4

Patient	Univariate analysis		Final multivariate model with 3 predictors	
	Patients, n	Appropriate treatment, n (%)	OR (95% CI)	p value
Overall	381	264 (69.3)		
Gender				
Male	196	129 (65.8)		0.149
Female	185	135 (73)		
Age				0.081
< 18 y	55	44 (80)		
18 y	326	220 (67.5)		
Tumour location				0.013
PHAEO	246	181 (73.6)		
PGL	127	77 (60.6)		
Metastasis				0.033
Yes	35	30 (85.7)	5.96 (1.93–18.46)	0.002
No	346	234 (67.6)		
Signs and symptoms				0.017
Present	353	247 (70)		
Absent	17	7 (41.2)		
Blood pressure				< 0.001
High	307	228 (74.3)	5.94 (3.11–11.33)	< 0.001
Normal	74	36 (48.6)		
Tachycardia				0.825
Present	189	132 (69.8)		
Absent	192	132 (68.8)		
Medical subspecialty				< 0.001
Endocrinology	226	183 (81)	4.14 (2.51–6.85)	< 0.001
Other	155	81 (52.3)		

CI = confidence interval; OR = odds ratio; PGL = paraganglioma; PHAEO = pheochromocytoma.

Table 5

Rate of prescription of a proper pharmacological treatment by each subspecialty. Those that managed less than or equal to 10 patients were not included.

Subspecialty	Patients, n	Appropriate treatment, n (%)
Endocrinology	226	183 (81)
Surgery	35	19 (54.3)
Internal medicine	24	14 (58.3)
Cardiology	21	9 (42.9)
Family medicine	18	2 (11.1)
Nephrology	18	16 (88.9)
Oncology	15	7 (46.7)
Paediatrics	14	11 (78.6)

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 6

Association between the characteristics of patients with hormonally functional PHAEO/PGL who were managed by endocrinologists and the prescription of proper pharmacological treatment.

Patient characteristics	Univariate analysis		
	Patients, n	Appropriate treatment, n (%)	p value
Overall	226	183 (81)	
Gender			0.499
Male	114	90 (78.9)	
Female	112	93 (83)	
Age			0.793
< 18 y	26	22 (84.6)	
≥ 18 y	200	161 (80.5)	
Tumour location			0.848
PHAEO	164	133 (81.1)	
PGL	59	47 (79.7)	
Metastasis			0.028
Yes	19	19 (100)	
No	207	164 (79.2)	
Signs and symptoms			0.051
Present	209	170 (81.3)	
Absent	8	4 (50)	
Blood pressure			0.001
High	185	158 (85.4)	
Normal	41	25 (61)	
Tachycardia			1,000
Present	113	92 (81.4)	
Absent	113	91 (80.5)	

PGL = paraganglioma; PHAEO = pheochromocytoma.