Journal of the Endocrine Society, 2021, Vol. 5, No. 10, 1–7
doi:10.1210/jendso/bvab073
Clinical Research Article

Clinical Research Article

Clinical Presentation and Perioperative Management of Pheochromocytomas and Paragangliomas: A 4-Decade Experience

Thomas Uslar,[1,2,3,4,*] Ignacio F. San Francisco,[2,5,*] Roberto Olmos,[1,2,3,4] Stefano Macchiavelo,[1] Alvaro Zuñiga,[2,3,5] Pablo Rojas,[2,5] Marcelo Garrido,[2,6] Alvaro Huete,[2,3,7] Gonzalo P. Mendez,[2,3,8] Ignacio Cortinez,[2,3,9] José Tomás Zemelman,[2] Joaquín Cifuentes,[2] Fernando Castro,[2] Daniela Olivari,[2] José Miguel Domínguez,[1,2,4] Eugenio Arteaga,[1,2,4] Carlos E. Fardella,[1,2,4] Gloria Valdés,[1,2,10] Rodrigo Tagle,[1,2,10] and Rene Baudrand[1,2,3,4]

[1]Departamento de Endocrinología, Diagonal Paraguay 362, 8330077, Santiago, Chile; [2]Facultad de Medicina, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, 8330077, Santiago, Chile; [3]Programa de Trastornos Suprarrenales, Diagonal Paraguay 362, 8330077, Santiago, Chile; [4]Centro Traslacional en Endocrinología (CETREN-UC), Diagonal Paraguay 362, 8330077, Santiago, Chile; [5]Departamento de Urología, Diagonal Paraguay 362, 8330077, Santiago, Chile; [6]Departamento de Hemato-Oncología, Diagonal Paraguay 362, 8330077, Santiago, Chile; [7]Departamento de Radiología, Diagonal Paraguay 362, 8330077, Santiago, Chile; [8]Departamento de Anatomía Patológica, Diagonal Paraguay 362, 8330077, Santiago, Chile; [9]Departamento de Anestesiología, Diagonal Paraguay 362, 8330077, Santiago, Chile; and [10]Departamento de Nefrología, Diagonal Paraguay 362, 8330077, Santiago, Chile

ORCiD number: 0000-0001-7213-855X (T. Uslar); 0000-0002-7129-9543 (R. Olmos); 0000-0002-8746-1111 (A. Huete); 0000-0002-6467-8414 (F. Castro); 0000-0003-1053-3524 (D. Olivari); 0000-0002-6157-8055 (J. M. Domínguez); 0000-0002-8090-539X (E. Arteaga); 0000-0002-5255-5740 (G. Valdés), 0000-0002-8655-4957 (R. Baudrand).

*These authors contributed equally to this work.

Abbreviation: PPGL, pheochromocytoma and paraganglioma.

Received: 10 February 2021; Editorial Decision: 15 April 2021; First Published Online: 22 April 2021; Corrected and Typeset: 4 August 2021.

Abstract

Purpose: Latin American reports on pheochromocytomas and paragangliomas (PPGLs) are scarce. Recent studies demonstrate changes in clinical presentation and management of these patients. Herein, we assessed the main characteristics of PPGL patients in our academic center over the past 4 decades.

Methods: Demographic, clinical, biochemical, and perioperative data from 105 PPGL patients were retrospectively and prospectively collected over the 1980–2019 period. Data were organized into 4 periods by decade.

ISSN 2472-1972

Results: Age at diagnosis, gender, tumor size and percentage of bilaterality, percentage of paragangliomas, and metastases remained stable across the 4 decades. The proportion of genetic testing and incidentalomas increased in recent decades (all $P < 0.001$). Therefore, we compared PPGLs diagnosed as incidentalomas (36%) with those clinically suspected (64%). Incidentalomas had fewer adrenergic symptoms (38 vs. 62%; $P < 0.001$) and lower rates of hypertension (64% vs. 80%; $P = 0.01$) and hypertensive crisis (28% vs. 44%; $P = 0.02$); also, they had lower functionality (79% vs. 100%; $P = 0.01$) and lower catecholamines levels (8.4-fold vs. 12.5-fold above upper cutoffs; $P = 0.04$). Regarding management of all PPGLs over the decades, we observed significant increases in both perioperative doxazosin dose ($P = 0.003$) and laparoscopic approach rates ($P < 0.001$), along with a decrease in the length of hospital stays ($P = 0.007$).
Conclusions: We observed a change in the clinical presentation of PPGL in recent decades, with a marked increase in incidental cases and milder symptoms. The implementation of a multidisciplinary program for adrenal disorders in our institution has translated into more timely diagnoses, more genetic testing, and improvements in perioperative management.

Key Words: pheochromocytoma, paraganglioma, incidentaloma, PPGL, clinical presentation, neuroendocrine

Pheochromocytomas and paragangliomas (PPGLs) are neuroendocrine tumors that arise from chromaffin cells in the adrenal medulla or from neural precursors in extra-adrenal paraganglia, respectively [1]; PPGLs are fairly uncommon, with an estimated incidence ranging from 1 to 8 cases per million per year [2, 3]. Despite of their relatively low incidence, PPGLs can be a serious condition and undiagnosed or untreated cases can be fatal [4]. Notably, studies speculate that a significant proportion of PPGLs are not detected in routine clinical practice, especially at early stages of the disease. In fact, it is estimated that 25% of PPGL patients remain undiagnosed during their lifetime [5]. Regarding PPGL pathophysiology, recent data indicate that these are the solid tumors with the highest percentage of hereditary predisposition, rising from about 10% to 40% in recent years, mainly because of expanded genetic testing. Familiar PPGL cases are secondary to mutations that affect one or more genes out of a growing list of more than 20 susceptibility genes [6].

Most epidemiological and descriptive studies have been conducted in the United States [7], Asia [2], or Europe [5, 8]. In contrast, the clinical characteristics of these tumors in Latin America are largely unknown. In fact, over the past decades, the clinical presentation of PPGLs has changed in several regions around the world [3, 9-12]. Currently, their diagnoses at asymptomatic stages of the disease have become more frequent because of the increase in incidental findings. On the other hand, the clinical management of PPGLs is complex and demands a multidisciplinary team of specialists including endocrinologists, nephrologists, urologists, anesthesiologists, and radiologists, among others. Recently, our institution developed a team of specialists and started a Program for Adrenal Disorders aiming to provide improved care for these patients.

Here, we present a Chilean single institutional registry of PPGLs. We analyze the changes in clinical presentation and perioperative management in our academic institution over the past 4 decades.

Materials and Methods

Patients

This was an observational retrospective and prospective study performed at the Hospital of the Pontificia Universidad Católica de Chile. Patient data were obtained from medical records dated between 1980 and 2019. Prospective data collection started in 2014 by the time our program for adrenal disorders was initiated. We collected demographic data, clinical presentation, and genetic testing as well as histopathological features, surgical protocols, type of surgery, length of hospital stay, and complications. Patients received preoperative preparation for at least 7 days with alpha-blockers up to the maximum tolerated dose. In the first 2 decades, only a few patients received phenoxybenzamine or prazosin, followed by the incorporation of doxazosin since the mid-1990s. Also, during the most recent decade, our institution incorporated a volume expansion with saline (100 mL/h over a 12-hour period), performed within 24 hours before the surgical procedure. Beta-blockers were added to control tachycardia. The therapeutic goal was to normalize arterial blood pressure, without orthostatic hypotension.

Adrenal incidentalomas were defined as adrenal tumors identified during a routine imaging analysis for unrelated causes. Patients were grouped into decades according to their date of surgery (1980-1989,1990-1999, 2000-2009, 2010-2019) and their clinical presentation (suspected PPGL, incidental PPGL, or screening in the context of familial disease). For the report of patient medical history, hypertensive crisis was defined as a systolic blood pressure >180 mm Hg and/or a diastolic blood pressure <120 mm Hg.

Catecholamines were measured using high-performance liquid chromatography for plasma and 24-hour urinary adrenaline, noradrenaline, metanephrine, and normetanephrine. The highest urine or plasma level was divided by the upper cutoffs to calculate a ratio. Functional PPGLs were defined as tumors with elevated levels of urine or fractionated plasma fractionated catecholamines or fractionated or total metanephrines above the normal limit of the respective reference range. Adrenergic tumors were defined by both an increase in metanephrine above upper cutoffs and a tumor-derived increase of urinary metanephrine of more than 5% the combined increase of normetanephrine and metanephrine. Noradrenergic tumors were defined by a tumor-derived increase in urinary normetanephrine with either a lack of increase in urinary free metanephrine or an increase of metanephrine less than 5% that of normetanephrine and metanephrine combined [1]. On the other hand, nonfunctional tumors were defined as plasma or urine levels within the reference range. Sample collection was made in the absence of known interfering drugs and during the follicular phase of the menstrual cycle. For urinary metanephrines, urine samples were collected in HCl-containing vials and immediately stored at 4°C. For plasma catecholamines, samples were taken after a 30-minute resting period in supine position and collected in ice-cold heparinized tubes. Selected samples were genetically tested by Invitae (https://www.invitae.com/en/about-invitae/) using next-generation sequencing in leukocyte samples from blood or saliva. Important considerations for testing were positive family history for PPGLs, bilateral disease, and younger age.

Ethics approval

The ethics committee of the School of Medicine of the Pontificia Universidad Católica de Chile reviewed and approved this study.

Statistical analysis

According to their distribution, data were expressed as percentage (%), average ± SD or median and range. Differences in categorical variables were assessed by the χ^2 test. Statistical differences between 2 groups were assessed by the Student *t* test. For comparison of >2 groups, we used ANOVA followed by Tukey or Dunn tests (parametric or nonparametric). All proportions considered missing values. All data were analyzed in SPSS v.21 and significance was set at $P < 0.05$. Normality of data was checked by the Kolmogorov-Smirnov test. We also applied a bootstrapping procedure with 1000 iterations when appropriate to deal with non-normality issues and outliers.

Results

A total of 131 surgeries were registered during the 1980 to 2019 period. Twenty-six patients were excluded because of missing data. Basic demographic and surgical characteristics of patients (n = 105) are summarized in Table 1. Fourteen patients were diagnosed in the first decade, 25 in the second, 27 in the third, and 39 in the fourth decade, showing an increase in the number of PPGLs diagnosed over the assessed period ($P < 0.001$). Age at diagnosis was 46 ± 19 years and patients were predominantly females (63%). Tumor size was 5.3 ± 2.2 cm, which remained consistent across the 4-decade period. Fifteen percent of patients had a bilateral procedure, 9% had paragangliomas, and 15% had metastatic disease, all of which were similar along the studied decades.

Remarkably, concerning the modality of PPGL discovery, the rate of incidental PPGLs increased from 0% in 1980 to 1989 to 53% in 2010 to 2019 ($P = 0.015$) (Table 1). The abovementioned switch in clinical presentation prompted us to analyze the characteristics of patients comparing incidentalomas vs. suspected symptomatic PPGLs. Table 2 shows that the classic triad that includes sweating, palpitations, and headaches was present in 53% of patients. Specifically, the percentages of palpitations and headaches were significantly higher in suspected PPGLs vs. incidentalomas ($P < 0.001$ for both). Similarly, pallor was more frequent among suspected PPGLs ($P = 0.037$). Other symptoms such as lipothymia and abdominal pain were more frequent in suspected PPGLs than in incidentalomas, respectively ($P = 0.043$ and $P < 0.001$).

Eighty-one percent of incidentalomas and 100% of suspected PPGLs were functioning PPGLs ($P = 0.003$), with suspected PPGLs having a significantly higher concentration of total metanephrines/catecholamines vs. incidental PPGLs ($P = 0.037$). Rates of hypertension and previous hypertension crisis were more frequent in suspected PPGLs ($P = 0.012$ and 0.018, respectively) (Table 2).

Regarding preoperative management of all PPGLs over the decades, 95% were prepared with doxazosin (Table 3). However, doxazosin dose increased from 2.7 ± 2.6 mg/day

Table 1. Patient and surgery characteristics by decade

Variable (units)	Decade					
	Total n = 105	1980-1989 (n = 14)	1990-1999 (n = 25)	2000-2009 (n = 27)	2010-2019 (n = 39)	*P* value
Age (y ± SD)	46 ± 19	53 ± 26	49 ± 24	46 ± 16	44 ± 16	0.547
Female (%)	63	78	52	70	59	0.302
Average tumor size (cm ± SD)	5.3 ± 2.2	5.7 ± 1.5	5.2 ± 2.7	4.8 ± 2.4	5.4 ± 1.8	0.749
Bilateral procedure (%)	15	0	17	13	15	0.115
Paraganglioma (%)	9	7	8	3	12	0.072
Metastasis (%)	15	0	22	9	16	0.468
Genetic test performed (%)	21	0	8	7	48	<0.001[a]
Incidentaloma (%)	35	0	18	23	53	0.015[a]

[a]*P* value lower than 0.05 was considered significant ($P < .05$).

Table 2. Clinical characteristics of patients with PPGL categorized by mode of discovery

Clinical (units)	Total n = 78	Incidentalomas (n = 28)	Suspected PPGL (n = 50)	*P* value
Sweating (%)	69	53	78	0.025[a]
Palpitation (%)	72	46	82	<0.001[a]
Headaches (%)	63	39	76	<0.001[a]
Classic triad (%)	53	40	62	0.001[a]
Pallor (%)	44	28	53	0.037[a]
Weight loss (%)	18	28	12	0.067
Anxiety (%)	17	14	18	0.673
Orthostatic symptoms (%)	26	21	28	0.52
Lipothymia (%)	19	7	26	0.043[a]
Abdominal pain (%)	29	57	14	<0.001[a]
No symptoms (%)	5	4	2	0.407
Laboratory				
Functional (%)	90	81	100	0.003[a]
Adrenergic (%)	47	35	56	0.138
Plasma adrenaline[a]	4.4 ± 5.7	3.5 ± 3.9	6.4 ± 8.2	0.291
Urinary adrenaline[a]	1.5 ± 1.7	1.5 ± 2.1	1.5 ± 1.2	0.965
Urinary metanephrine[a]	5.4 ± 8.7	2.6 ± 4.2	7.2 ± 10.4	0.055
Noradrenergic (%)	43	46	44	0.983
Plasma noradrenaline[a]	3.9 ± 4.8	3.7 ± 4.0	5.0 ± 6.6	0.608
Urinary noradrenaline[a]	6.7 ± 9.2	11.8 ± 12.4	3.1 ± 2.4	0.071
Urinary normetanephrine[a]	5.9 ± 6.0	5.1 ± 6.5	6.4 ± 5.6	0.449
Total metanephrines/catecholamines[a]	10.3 ± 11.1	8.0 ± 7.1	12.4 ± 8.9	0.037[a]
Medical history				
Overweight/obesity (%)	51	48	54	0.639
Hypertension (%)	72	64	80	0.012[a]
Previous hypertensive crisis (%)	36	28	44	0.018[b]
Median time as hypertensive before diagnosis (months, range)	8 (0-420)	12 (0-420)	9 (0-180)	0.651
Number of antihypertensive drugs (mean ± SD)	1.1 ± 1.0	1.0 ± 0.9	1.2 ± 1.0	0.326

Abbreviation: PPGL, pheochromocytoma and paraganglioma.
[a]Highest urinary metanephrine/normetanephrine and/or plasma/urinary catecholamine level divided by the upper level of the normal respective reference range.
[b]*P* value lower than 0.05 was considered significant ($P < .05$).

in the 2000 to 2009 decade to 8.0 ± 4.5 mg/day in the 2010 to 2019 decade ($P = 0.003$). The rate of laparoscopic surgeries increased from 28% in 1980 to 1989 to 84% in 2010 to 2019 ($P < 0.001$). The length of hospital stays was reduced from 10.0 days in 1980 to 1989 to 3.8 days in 2010 to 2019 ($P = 0.007$) with a 50% shorter length stays in laparoscopic vs. open surgery, despite similar tumor size (data not shown). The frequency of hypertensive

Table 3. Perioperative characteristics over 4 Decades

	Total n = 105	Decade				*P* value
		1980-1989 (n = 14)	1990-1999 (n = 25)	2000-2009 (n = 27)	2010-2019 (n = 39)	
Perioperative						
Preparation (%)	95	100	100	95	91	0.283
Doxazosin dose (mg, mean ± SD)	6.8 ± 4.3	NR	NR	2.7 ± 2.6	8.0 ± 4.5	0.003[a]
Right-sided procedure (%)	48	25	50	30	57	0.115
Laparoscopic surgeries (%)	62	28	32	67	84	<0.001[a]
Length of stays (days, mean ± SD)	9.2 ± 3.6	10.0 ± 8.9	7.9 ± 6.0	7.9 ± 6.0	3.8 ± 1.7	0.007[a]
Hypertensive crisis during surgery (%)	42	25	50	64	23	0.024[a]

[a]*P* value lower than 0.05 was considered significant ($P < .05$).

crisis during surgeries was reduced from 50% in 1990 to 2000 to 23% in 2010 to 2019 ($P = 0.024$). There were no perioperative deaths.

A family history of PPGLs was identified in 7.6% patients and 9.5% had a family history of genetic syndrome associated with PPGLs, all of which received genetic counseling; 75% accepted genetic testing. There was an increase in genetic testing analyses in the past decade (0% in 1980-1989 vs. 48% in 2010-2019; $P < 0.001$). Among the 22 genetic tests performed, we identified 59% disease-causing germline mutations. The most frequent mutations affected the *RET* (18%) and *SDHx* (18%) genes, followed by *VHL* (14%), *MAX* (5%), and *NF1* (4%). Nine patients (41%) displayed no alterations or variants of unknown significance; see details in Supplementary Table 1 [13]. Three of the included patients had PPGLs discovered because of mutation-based case detection testing.

Discussion

Our study evaluated the clinical presentation of 105 PPGL patients across 4 decades. During this period, we found a shift in clinical presentation toward incidental findings as well as an improvement in genetic screening and perioperative outcomes. To the best of our knowledge, only 2 small patient series have been previously reported in Argentina [14] and Colombia [15] (both in Spanish); therefore, this study is the largest PPGL registry in Latin America. Our findings are similar to previous studies regarding age at diagnosis [2], tumor size [16, 17], bilaterality, and prevalence of paragangliomas and metastatic cases [2, 3, 16, 17], suggesting no selection bias in our cohort. Interestingly, the number of patients with PPGLs diagnosed in previous decades was lower compared with the past decades, which highlights a better recognition of these conditions at our institution.

The most interesting finding in our study was the evolution of clinical presentation over time, shifting from a symptom-based to an incidental diagnosis from 0% in the 1980 to 1989 decade up to 53% in the 2010 to 2019 decade (Table 1). This is in line with a recent cohort study that postulates a switch in the clinical presentation of "modern era" pheochromocytomas [9], as opposed to the traditional diagnosis based on symptoms, especially by paroxysmal hypertension. A similar study by Kopetschke et al. [3] also reported a marked increase in incidentally discovered pheochromocytomas over time, increasing from <10% in from 1973 to 1984 to about 40% in from 1985 to 1996. Authors speculate this increase could be attributed to (1) increased availability of abdominal ultrasounds, magnetic resonance imaging, and computed tomography scans; (2) better access, health education, and disease awareness; and (3) other cohorts also increase their detection by mutational "screenings"; a point topic further discussed later.

As previously postulated by others [9], we anticipated that incidentally discovered PPGLs would display a different behavior compared with those discovered by symptoms. As expected, incidental findings had fewer symptoms such as the classic triad, pallor and lipothymia (Table 2). Similar trends were reported in the study of Falhammer et al. [16], and Gruber et al. [9]. The latter investigators found that tumors discovered because of symptoms were larger and more biochemically active, suggesting they were discovered later in their natural history [9]. We found more biochemical activity in PPGL discovered by symptoms, but no difference in tumoral size, which is probably explained by our limited number of cases. Early detection and treatment may prevent morbidity, malignant progression, and mortality attributed to PPGLs, especially considering autopsy series with large proportions of undiagnosed PPGLs as the cause of death [18, 19].

Surgical removal is the standard of care for most PPGL cases. In general, small tumors (<6 cm) are removed by laparoscopic surgery, whereas for larger tumors open surgery is the recommended choice [1]. Before surgery, current recommendations include management with alpha-blockers

and volume expansion using saline, aiming to prevent hemodynamic intraoperative complications during surgery derived from a massive catecholamine release while the tumor is in situ and a marked blood pressure fall that starts when large veins are sectioned. In 2014, our center started a preoperative protocol similar to one recently published [20] that also involves monitoring patient blood pressure/electrocardiogram/glucose during and after surgery via arterial catheters. We found fewer hypertensive crises over the past decade, compared with similar cohorts that did not apply such preparation protocols [21].

Furthermore, in agreement with previous reports [22, 23], our data demonstrate a progressive increase of laparoscopic surgeries over time that has translated into shorter hospitalizations. Moreover, other factors may have influenced our results such as pain control with the introduction of remifentanil. This drug has allowed the administration of larger doses of intraoperative opioids, improving hemodynamic stability associated with nociceptive stimuli, without residual effects. Remarkably, our 4-decade study reports no deaths that could be attributed to an inappropriate preparation before and during surgery.

In recent years, major advances in sequencing techniques have allowed the implementation of next-generation sequencing as the standard tool for genetic profiling of PPGL patients [24]. This technique offers a more accurate prognosis and a risk-adjusted management regarding diagnostic workup, surgery, clinical follow-up, and genetic counseling [19, 25]. Unfortunately, genetic tests for most PPGLs' molecular drivers are not available in most Latin American countries, which increases costs and complexity of patient's workup. However, in our experience this can be a cost-effective process, considering the proportion of positive genetic tests in our cohort, the impact of PPGLs discovered because of mutation-based case detection testing and the individualization of follow-up. Indeed, in agreement with the current literature [26], our center has seen a marked increase in genetic testing in recent decades. Compared with other cohorts [3, 9], the proportion of genetic tests performed was similar, especially in the past decade. However, we found a higher proportion of disease-causing germline mutations compared with those cohorts (59% compared with 24.4% and 27.4%, respectively). This could be explained by more rigorous criteria when selecting patients, such as positive family history, bilateral disease, younger age, and noradrenergic extra-adrenal tumors.

Just as we have found a change in clinical presentation from PPGLs discovered based on symptoms to incidental findings on imaging, we expect an increase in mutation-based case detection in the coming decades . Notably, others have shown better outcomes related to the management of presymptomatic SDH-carrier patients such as less surgery frequency, lower persistent and/or unresectable disease, metastases, radiotherapy, and disease-related mortality [27, 28]. In the future, to achieve better recognition of genetic predisposed PPGLs in our center, efforts will be made to implement SDH immunohistochemistry in tumor tissue to further guide the identification of patients at risk for familial succinate dehydrogenase-related PPGLs [29].

The main strength of this study is that patients were managed by a multidisciplinary team including specialized endocrine surgeons, anesthesiologists, endocrinologists, radiologists, and pathologists, in a single center. Limitations are mainly derived from the retrospective nature of our study; for some patients, medical records were missing or incomplete especially during the first decade (1980-1989).

In conclusion, we found a shift in clinical presentation from symptom-based diagnoses to incidental cases probably linked to early diagnosis. We increased genetic testing and achieved better perioperative outcomes over the decades related to the development of a multidisciplinary management program within our institution. We confirm our Hispanic patients' characteristics are similar to those described in previous international reports.

Acknowledgements

None.

Financial Support: Fondecyt grant #1190419 (R.B., R.O., M.G., A.H.).

Additional Information

Correspondence: René Baudrand, MD, Pontificia Universidad Católica de Chile, Diagonal Paraguay 362, 4th FL, RM, Santiago, Chile, 8330077. Email: rbaudran@uc.cl.

Disclosures: The authors have nothing to disclose.

Data Availability: All data generated or analyzed during this study are included in this published article.

References

1. Lenders JW, Duh QY, Eisenhofer G, et al.; Endocrine Society. Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2014;**99**(6):1915-1942.
2. Kim JH, Moon H, Noh J, Lee J, Kim SG. Epidemiology and prognosis of pheochromocytoma/paraganglioma in Korea: a nationwide study based on the national health insurance service. *Endocrinol Metab*. 2020;**35**:157.
3. Kopetschke R, Slisko M, Kilisli A, et al. Frequent incidental discovery of phaeochromocytoma: data from a German cohort of 201 phaeochromocytoma. *Eur J Endocrinol*. 2009;**161**(2):355-361.
4. Riester A, Weismann D, Quinkler M, et al. Life-threatening events in patients with pheochromocytoma. *Eur J Endocrinol*. 2015;**173**(6):757-764.

5. Khorram-Manesh A, Ahlman H, Nilsson O, Odén A, Jansson S. Mortality associated with pheochromocytoma in a large Swedish cohort. *Eur J Surg Oncol*. 2004;**30**(5):556-559.
6. Fishbein L, Nathanson KL. Pheochromocytoma and paraganglioma: understanding the complexities of the genetic background. *Cancer Genet*. 2012;**205**(1-2):1-11.
7. Ariton M, Juan CS, AvRuskin TW. Pheochromocytoma: clinical observations from a Brooklyn tertiary hospital. *Endocr Pract*. 2000;**6**(3):249-252.
8. Berends AMA, Buitenwerf E, de Krijger RR, et al. Incidence of pheochromocytoma and sympathetic paraganglioma in the Netherlands: a nationwide study and systematic review. *Eur J Intern Med*. 2018;**51**:68-73.
9. Gruber LM, Hartman RP, Thompson GB, et al. Pheochromocytoma characteristics and behavior differ depending on method of discovery. *J Clin Endocrinol Metab*. 2019;**104**(5):1386-1393.
10. Amar L, Servais A, Gimenez-Roqueplo AP, Zinzindohoue F, Chatellier G, Plouin PF. Year of diagnosis, features at presentation, and risk of recurrence in patients with pheochromocytoma or secreting paraganglioma. *J Clin Endocrinol Metab*. 2005;**90**(4):2110-2116.
11. Chen X, Hu L, Liu C, Ni G, Zhang Y. Tumor characteristics and surgical outcome in incidentally discovered pheochromocytomas and paragangliomas. *Endocr Connect*. 2018;**7**:1142-1149.
12. Noshiro T, Shimizu K, Watanabe T, et al. Changes in clinical features and long-term prognosis in patients with pheochromocytoma. *Am J Hypertens*. 2000;**13**(1 Pt 1):35-43.
13. Supplementary Table 1.pdf. https://figshare.com/articles/figure/Supplementary_Table_S1_pdf/14327231/1.
14. Santoro S, Palma Y, Barontini M, Amicucci R, Lamy R, Lupi S. Feocromocitoma y paragangliomas: experiencia de un hospital de Buenos Aires. *Rev Argent Cardiol*. 2015;**83**:136-140.
15. Navarro EP, Osejo MC, Casas LÁ, Arango LG, Guzmán G. Experiencia en el manejo de feocromocitoma en los últimos 10 años: serie de casos. *Revista ACE*. 2016;**3**(3):33-36.
16. Falhammar H, Kjellman M, Calissendorff J. Initial clinical presentation and spectrum of pheochromocytoma: a study of 94 cases from a single center. *Endocr Connect*. 2018;**7**:186-192.
17. Falhammar H, Kjellman M, Calissendorff J. Treatment and outcomes in pheochromocytomas and paragangliomas: a study of 110 cases from a single center. *Endocrine*. 2018;**62**(3):566-575.
18. McNeil AR, Blok BH, Koelmeyer TD, Burke MP, Hilton JM. Phaeochromocytomas discovered during coronial autopsies in Sydney, Melbourne and Auckland. *Aust N Z J Med*. 2000;**30**(6):648-652.
19. Eisenhofer G, Klink B, Richter S, Lenders JW, Robledo M. Metabologenomics of phaeochromocytoma and paraganglioma: an integrated approach for personalised biochemical and genetic testing. *Clin Biochem Rev*. 2017;**38**(2):69-100.
20. Berends A, Kerstens M, Lenders J, Timmers H. Approach to the patient: perioperative management of the patient with pheochromocytoma or sympathetic paraganglioma. *J Clin Endocrinol Metab* 2020;**105**. doi:10.1210/clinem/dgaa441.
21. Buisset C, Guerin C, Cungi PJ, et al. Pheochromocytoma surgery without systematic preoperative pharmacological preparation: insights from a referral tertiary center experience. *Surg Endosc*. 2021;**35**(2):728-735.
22. Toniato A, Boschin IM, Opocher G, Guolo A, Pelizzo M, Mantero F. Is the laparoscopic adrenalectomy for pheochromocytoma the best treatment? *Surgery*. 2007;**141**(6):723-727.
23. Kercher KW, Novitsky YW, Park A, Matthews BD, Litwin DE, Heniford BT. Laparoscopic curative resection of pheochromocytomas. *Ann Surg*. 2005;**241**(6):919-26; discussion 926.
24. Alrezk R, Suarez A, Tena I, Pacak K. Update of pheochromocytoma syndromes: genetics, biochemical evaluation, and imaging. *Front Endocrinol (Lausanne)*. 2018;**9**:515.
25. Crona J, Taïeb D, Pacak K. New perspectives on pheochromocytoma and paraganglioma: toward a molecular classification. *Endocr Rev*. 2017;**38**(6):489-515.
26. Asban A, Kluijfhout WP, Drake FT, Beninato T, Wang E, Chomsky-Higgins K, et al. Trends of genetic screening in patients with pheochromocytoma and paraganglioma: 15-year experience in a high-volume tertiary referral center. *J Surg Oncol*. 2018;**117**:1217-1222.
27. Buffet A, Ben Aim L, Leboulleux S, et al.; French Group of Endocrine Tumors (GTE) and COMETE Network. Positive impact of genetic test on the management and outcome of patients with paraganglioma and/or pheochromocytoma. *J Clin Endocrinol Metab*. 2019;**104**(4):1109-1118.
28. Martins RG, Cunha N, Simões H, et al. Surveillance of succinate dehydrogenase gene mutation carriers: insights from a nationwide cohort. *Clin Endocrinol (Oxf)*. 2020;**92**(6):545-553.
29. van Nederveen FH, Gaal J, Favier J, et al. An immunohistochemical procedure to detect patients with paraganglioma and phaeochromocytoma with germline SDHB, SDHC, or SDHD gene mutations: a retrospective and prospective analysis. *Lancet Oncol*. 2009;**10**(8):764-771.