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Pediatric Patients with Pheochromocytoma and Paraganglioma should have routine preoperative genetic testing for common susceptibility genes and imaging to detect extra-adrenal and metastatic tumors

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Abstract

Background—Pediatric pheochromocytomas and paragangliomas (PC/PGLs) are rare with limited data as to what the optimal management approach is. The aim of this study was to determine the role of genetic testing and imaging to detect extra-adrenal and/or metastatic tumors in pediatric PC/PGLs.

Methods—A retrospective study of 55 patients diagnosed at < 21 years of age with PC/PGLs was performed with analysis of data on genetic testing and multimodal imaging.

Results—Eighty percent of patients (n=44/55) had a germline mutation. The majority were found to have either *VHL* (38%) or *SDHB* (25.4%) mutation. PC was present in 67% (n=37/55) of patients and was bilateral in 51.3% (n=19/37). The majority of patients with bilateral PC had *VHL* (79%). Abdominal PGL was present in 21.8% (n=12/55), head and neck PGL in 11% (n=6/55) and thoracic PGL in 3.6% (n=2/55) of patients. For PGL, *SDHx* accounted for 72% (n=13/18) of mutations. The rate of malignancy was 16.4% (n=9/55), 55.5% had *SDHB* mutations. In two-thirds of patients, functional imaging identified either extra-adrenal PGL and/or metastatic disease.

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Conclusions—The majority of pediatric patients with PC/PGL have germline mutations. Therefore, all pediatric patients with PC/PGLs require genetic testing and imaging to detect extra-adrenal PGL and metastatic disease to guide treatment and follow up.

Keywords

pheochromocytoma; paraganglioma; pediatric; genetic testing; imaging

Introduction

Pheochromocytomas and paragangliomas (PC/PGL) are rare neoplasms in the pediatric population, arising from the neural crest derived chromaffin cells of the adrenal medulla and extra-adrenal ganglion. The incidence of PC/PGL in the pediatric population is 0.2–0.3 cases per million persons. PC and the majority of abdominal PGL of sympathetic ganglia origin are functionally active with hypersecretion of catecholamines and their metabolites. Signs and symptoms of catecholamine excess include hypertension, headaches and/or palpitations. PGLs of the head and neck are derived from parasympathetic ganglia and are commonly non-functioning¹.

More than 14 germline and somatic mutations have been identified in association with PC/PGLs². Common susceptibility genes for PC/PGLs include germline mutations in *VHL*, *SDHx* (*SDHB* and *SDHD*), *RET*, and *NFI*. Previous studies have identified that mutations in these genes may be present in up to 70% of individuals younger than 18 years who have PC/PGL^{3,4}. In the pediatric population, about one-third of patients with PC/PGL present with bilateral adrenal PC and 18 to 22% have extra-adrenal PGL^{5,6}. The rate of malignancy reported has varied depending on the study and ranges from 12–56%⁷. The rate of malignancy also varies depending on the presence of the specific germline mutation. For example, King and colleagues⁸ describing metastatic PC/PGL associated with *SDHB* germline mutations in 71.9% of patients. A recent Endocrine Society Practice Guideline recommended considering genetic testing in all patients with PC/PGLs, although the clinical utility may be limited in individuals with unilateral PC, no family history and no evidence of metastatic disease. In addition, computed tomography (CT) was recommended as first line imaging for a new diagnosis of PC/PGL and functional imaging to evaluate for metastatic disease⁹.

The aim of this study was to determine the role of genetic testing and imaging to detect extra-adrenal and/or metastatic tumors in pediatric PC/PGLs.

Methods and Materials

A retrospective analysis in pediatric patients (< 21 years of age at diagnosis) with PC/PGLs was conducted. All patients were enrolled in clinical protocols (NCT00004847, NCT00062166, and NCT01005654) at the National Institutes of Health Clinical Center after written informed consent was obtained from the patient or their guardians. The studies were approved by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) and National Cancer Institutes (NCI) institutional review board.

Inclusion criteria for the current study included patients ≥ 21 years of age with biochemical, histologic and/or imaging evidence of PC/PGLs. Demographic data, including age at diagnosis, clinical presentation, family history, biochemical data, imaging, and pathology results were obtained from the electronic medical and radiology records. Biochemical data included plasma free metanephrine and normetanephrine, 24-hour urine fractionated metanephrine and normetanephrine, total 24-hour urine metanephrine, and plasma and 24-hour urine dopamine. Imaging studies included contrast-enhanced anatomic imaging with CT and/or magnetic resonance imaging (MRI) and functional imaging; ^{18}F -fluorodeoxyglucose (^{18}F -FDG) PET/CT, ^{18}F -L-dihydroxyphenylalanine (^{18}F -FDOPA) PET/CT, ^{18}F -Fluorodopamine (^{18}F -FDA) PET/CT, $^{1-123}\text{I}$ metaiodobenzylguanidine ($^{1-123}\text{I}$ MIBG), and/or ^{68}Ga -DOTATATE PET/CT. Tumors were classified as solitary or multiple, PC laterality (unilateral or bilateral), bilateral at initial presentation (synchronous) or developing a contralateral PC after initial presentation (metachronous), recurrence, defined as tumor recurrence at previously resected site or developing new primary at different anatomic location that was not metastatic disease. Recurrent lesions were biochemically active and/or patients were symptomatic. Primary tumor location was defined as adrenal or extra-adrenal abdominal, head and neck or thoracic. Tumors were classified as benign or malignant, based on metastasis to lymph nodes or distant sites where chromaffin cells are not present.

Genetic testing in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory for PC/PGL susceptibility genes (*VHL*, *RET*, *SDH A-D* and *MAX*) was performed. Recurrence time was defined as presentation of new lesion(s) requiring operative intervention in months from the last operative intervention. CT and/or MRI and at least one functional imaging modality (^{18}F -FDG PET/CT, $^{1-123}\text{I}$ MIBG, ^{18}F -FDOPA PET/CT, ^{68}Ga -DOTATATE PET/CT, and/or ^{18}F -FDA PET) results were analyzed for the detection of number of tumors and sites of extra-adrenal disease. This was compared to the number of tumors confirmed on pathology and the detection rate calculated. Skeletal metastasis was evaluated based on anatomic and functional imaging and not based on pathological confirmation.

Results

Genetic Findings and Rate of Extra-adrenal and Metastatic PC/PGLs

Fifty-five pediatric patients with PC/PGLs were included with a mean age at diagnosis of 13.6 ± 5.03 years. The clinical and genetic features of the study cohort are summarized in Table 1. In Figure 1, the frequency of distribution of PC/PGLs by age category and the germline mutation status is summarized. Genetic testing revealed that 80% of patients had a germline mutation in a known susceptibility gene; *VHL* 38%, *SDHB* 25.4%, *SDHD* 7.2%, *RET* 5.4%, *SDHA* 1.8%, *NFI* 1.8% and *MAX* 1.8%. In 20% ($n=11/55$) of patients, there was no known germline mutation identified. In the entire cohort, 40% ($n=22/55$) of patients had a family history and of those with a family history, all had a germline mutation. Of patients without a family history, 66.7% had a germline mutation ($n=22/33$), *VHL* ($n=5/22$), *RET* ($n=3/22$), *SDHB* ($n=9/22$), *SDHD* ($n=3/22$), *SDHA* ($n=1/22$), and *NFI* ($n=1/22$).

At initial presentation, PC was present in 67% (n=37/55) of patients and 21.6% (n=8/37) presented with bilateral synchronous PCs. Six of these patients with bilateral synchronous PC were found to have a *VHL* germline mutation. The remaining two patients had a germline *SDHD* and no known germline mutation. Eight percent (n=3/37) of patients with PC presented with metastatic disease. Solitary PC with no family history or evidence of metastatic disease was present in 35.1% (n=13/37) of patients. Of these patients, 61.5% (n=8/13) had a germline mutation. *VHL* and *RET* were the most common mutation in patients with a solitary PC and no family history, each with 37.5% (n=3/8). Thirty percent (n=11/37) of patients with PCs developed metachronous, contralateral PCs over a span of 1.3 to 10 years (mean 2.7 ± 1.1 years). Ultimately, 51.3% (n=19/37) of pediatric patients had either bilateral synchronous or metachronous PCs. The majority of these patients (15/19) were found to have a *VHL* germline mutation (Table 2). Six patients with *VHL* and PC had recurrences. Four recurrences were a new primary at an extra-adrenal location (three abdominal and one thoracic PGL) and two in the remnant adrenal gland after partial adrenalectomy. Recurrence occurred over a span of 6 months to 16 years (mean 8.1 ± 6.2 years). The patient who recurred within 6 months had positive margins at the initial operation.

Eighteen patients at initial presentation had a PGLs. Extra-adrenal abdominal PGL were present in 21.8% (n=12/55). Six patients presented with head and neck PGL. Two patients with previous PC/PGL resections presented with thoracic PGLs during follow-up. *SDHx* germline mutations were identified in 72% (n=13/18) of patients with PGLs (*SDHB* 55.5%, n=10/18; *SDHD* 16.6%, n=3/18). In the remaining five patients, one had a *VHL* mutation, and four patients had no germline mutation identified. Seventy-two percent (n=13/18) of patients presenting with extra-adrenal and extra-abdominal PGLs had no family history.

The rate of malignancy was 16.4% (n=9/55). Five patients had *SDHB* germline mutations, one patient had a *SDHA* germline mutation, and three patients had no known germline mutation. Three of the nine patients initially presented with a PC, four with extra-adrenal abdominal PGLs and two with head and neck PGLs. Five of nine patients had skeletal metastasis; three patients had *SDHB* mutations. Of the remaining two patients one had *SDHA* mutation and one with no known mutation. The other four patients had evidence of metastasis based on pathology (two had germline *SDHB* mutations).

Imaging Study Results

Imaging studies included anatomic imaging with contrast-enhanced CT and/or MRI, and functional imaging with one or more of the following modalities: ^{18}F -FDG, ^{18}F -FDOPA, ^{18}F -FDA PET/CT, $^{1-123}\text{I}$ MIBG, and ^{68}Ga -DOTATATE PET/CT. Preoperative imaging studies were analyzed in the detection of PC/PGL based on histologically confirmed PC/PGLs of patients who had an operative intervention at our institution (Tables 3 and 4). CT identified all PC and extra-abdominal PGLs, but had a 68.2% detection rate for abdominal PGLs. MRI had a detection rate of 92.6% for PC, 74% for abdominal PGLs and 100% for extra-abdominal PGLs. ^{18}F -FDG PET/CT identified all extra-abdominal disease and had a higher detection rate for extra-adrenal PGLs compared to all other imaging modalities (Table 4).

¹⁸F-FDG PET/CT detected more skeletal metastasis when compared to ^{I-123}MIBG. Five of nine (55%) patients with malignant PC/PGL were found to have skeletal metastases by imaging. ¹⁸F-FDG PET/CT identified skeletal metastases in all five patients. Two of the five patients with increased focal skeletal avidity on ¹⁸F-FDG PET/CT did not have increased uptake on ^{I-123}MIBG. ^{I-123}MIBG failed to identify skeletal metastasis in two patients with *SDHB* mutation. Two of five patients with skeletal metastasis had additional functional imaging in addition to ¹⁸F-FDG PET/CT: one ¹⁸F-FDOPA and one ¹⁸F-FDA PET/CT. Both had the same findings as ¹⁸F-FDG PET/CT. The number of studies performed for the other functional imaging modalities (¹⁸F-FDOPA, ¹⁸F-FDA PET/CT, ⁶⁸Ga-DOTATATE PET/CT) was less in comparison to ¹⁸F-FDG PET/CT and ^{I-123}MIBG, however all modalities did identify a subset of known PC and PGL lesions.

Discussion

PC/PGL in the pediatric population is rare. In this study, 80% of pediatric patients with PC/PGL were found to have a germline mutation in a known susceptibility gene. Of patients who had no family history, 66% had a germline mutation. Solitary PC with no family history or evidence of metastatic disease was present in 35.1% (n=13/37) of patients with pheochromocytoma. Of those patients, 61.5% (n=8/13) had a germline mutation, with *VHL* and *RET* mutations in three patients each and *SDHx* in the remaining two. ¹⁸F-FDG PET/CT detected more extra-adrenal tumors as compared to all other imaging modalities. ¹⁸F-FDG PET/CT had comparable number of scans performed to ^{I-123}MIBG and was superior when compared to ^{I-123}MIBG for detecting extra-adrenal PGL and skeletal metastasis. A small number of other functional studies were performed (¹⁸F-FDOPA, ¹⁸F-FDA PET/CT), which also detected skeletal metastasis.

A recent Endocrine Society Practice Guideline recommended considering genetic testing in patients with PC/PGL, but there were no specific recommendations for the pediatric population. In addition, the guideline also stated it may not be a necessity to perform genetic testing in individuals with solitary PC or in those who do not have a family history or evidence of metastatic disease⁹. Our data supports that in the pediatric population, which is defined as individuals younger than 21 in this study, all patients presenting with a PC/PGL should undergo genetic testing, including patients who present with a solitary PC and no family history or evidence of metastasis. This is because approximately two-thirds of patients with a solitary PC with no family history or evidence of metastatic disease had a germline mutation. This finding underscores the importance of genetic testing in the pediatric population regardless of findings of a solitary PC or the lack of family history.

A comprehensive family history for PC/PGL and clinical manifestations (MEN 2 and NF1) are indispensable when evaluating for which genetic test to perform. For patients without a family history, sequential genetic testing based on biochemical profile of catecholamine excess, age at presentation, tumor site, and tumor multiplicity and laterality have been previously proposed^{9,10}. We believe our data supports testing for all known susceptibility genes given the high carrier rate identified in the pediatric population. Of the many susceptibility genes, *VHL* germline mutations have been described as the most common in pediatric PC/PGL, with patients as young as five years of age developing PC¹¹. *SDHB* is the

most common genetic mutation in PGL³ and should be investigated in individuals presenting with abdominal PGL and metastatic disease. Head and neck PGLs are frequently associated with *SDHD* mutations¹². Head and neck PGL have a low rate of metastatic disease, although this depends on the tumor location (e.g. the rate of metastatic disease is 1.4% for carotid body PGL as compared to 10% for vagal PGL)¹³. In our cohort, one-third of patients with head and neck PGLs had metastatic disease, which was diagnosed on functional imaging alone. Patients with multiple endocrine neoplasia type 2 (MEN2), caused by a mutation in the *RET* proto-oncogene, present or develop PC in 50% of cases¹⁴. Rarely, patients with neurofibromatosis type 1 (NF1) present with a PC (1–5.7% of patients). This syndrome is caused by a mutation in the *NFI* tumor suppressor gene¹⁵ and is commonly diagnosed based on clinical criteria, which includes the presence of six or more café-au-lait spots, two or more neurofibromas and the presence of axillary or inguinal freckles^{16,17}. *MAX*, myc-associated factor X, mutation was recently characterized¹⁸. The gene encodes proteins that are part of a family of transcription factors. A recent analysis of a large cohort of patients with PC/PGL evaluated for *MAX* mutations and only 1.12% were positive for the mutation¹⁹.

Our study results showing a high rate of germline mutations in PC/PGL susceptibility genes in pediatric patients with PC/PGL are consistent with most studies. Hammond and colleagues²⁰ identified germline mutations in 100% of seven patients with PC/PGL. Other investigators have also found a high rate of germline mutations, up to 70 %, in patients under the age of 18 years^{3,4,21}. Our data suggest that all pediatric patients presenting under age 21 with a PC/PGL should have genetic testing performed for common susceptibility genes. This is also supported by the fact that 60% of the pediatric patients did not have a family history. One important factor previously used to support for sequential susceptibility gene testing for PC/PGL was the cost of genetic testing. However, with advances in next generation sequencing allowing for simultaneous testing for mutations/deletions in multiple susceptibility genes such an approach could be cost-effective in pediatric patients with PC/PGL.

Contrast enhanced CT is recommended as the first-line imaging modality for evaluation of PC/PGL with a reported sensitivity of 88–100%, while MRI has been recommended for detection of head and neck PGL, and ¹⁸F-FDG PET/CT for metastatic disease^{9,22}. Our results support previously described findings that found ¹⁸F-FDG PET/CT had higher sensitivity in comparison to ¹⁻¹²³MIBG for detecting metastatic lesions, specifically skeletal metastasis²² as well as recurrent disease²³. Functional imaging identified additional sites of disease not identified on anatomical imaging, specifically skeletal metastasis. It is necessary to have both anatomic and functional imaging when evaluating all pediatric patients who present with PC/PGL.

One of the main limitations of the current study is that we are a referral center and thus our study has a selection bias. However, individuals with no family history, solitary tumors, or only symptoms and/or biochemical evidence of a PC/PGL without localization are also evaluated at our institution. This is evident in that 60% of the study cohort had no family history and 74.5% had a solitary tumor at presentation, suggesting our findings would be applicable to the pediatric population with PC/PGL. Furthermore, the number of patients in the cohort is small but pediatric PC/PGL is rare. A limited number of functional imaging

studies were performed, excluding ^{18}F -FDG PET/CT and ^{123}I -MIBG, to draw definitive conclusions about the specific functional imaging study that is best for detecting extra-adrenal or metastatic disease.

In summary, we found that pediatric patients with PC/PGL have a high rate of germline mutations despite a lack of family history. Given these findings, pediatric patients with PC/PGL would benefit from genetic screening for all known susceptibility genes. Furthermore, these patients require multimodal imaging including anatomical and functional imaging to detect all disease sites for appropriate treatment selection.

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References

1. Waguespack SG, Rich T, Grubbs E, et al. A current review of the etiology, diagnosis, and treatment of pediatric pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab.* 2010; 95:2023–2037. [PubMed: 20215394]
2. Curras-Freixes M, Inglada-Perez L, Mancikova V, et al. Recommendations for somatic and germline genetic testing of single pheochromocytoma and paraganglioma based on findings from a series of 329 patients. *J Med Genet.* 2015; 52:647–656. [PubMed: 26269449]
3. Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med.* 2002; 346:1459–1466. [PubMed: 12000816]
4. Cascon A, Inglada-Perez L, Comino-Mendez I, et al. Genetics of pheochromocytoma and paraganglioma in Spanish pediatric patients. *Endocr Relat Cancer.* 2013; 20:L1–L6. [PubMed: 23404858]
5. Barontini M, Levin G, Sanso G. Characteristics of pheochromocytoma in a 4- to 20-year-old population. *Ann N Y Acad Sci.* 2006; 1073:30–37. [PubMed: 17102069]
6. Beltsevich DG, Kuznetsov NS, Kazaryan AM, et al. Pheochromocytoma surgery: epidemiologic peculiarities in children. *World J Surg.* 2004; 28:592–596. [PubMed: 15366751]
7. Armstrong R, Sridhar M, Greenhalgh KL, et al. Pheochromocytoma in children. *Arch Dis Child.* 2008; 93:899–904. [PubMed: 18499773]
8. King KS, Prodanov T, Kantorovich V, et al. Metastatic pheochromocytoma/paraganglioma related to primary tumor development in childhood or adolescence: significant link to SDHB mutations. *J Clin Oncol.* 2011; 29:4137–4142. [PubMed: 21969497]
9. Lenders JW, Duh QY, Eisenhofer G, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab.* 2014; 99:1915–1942. [PubMed: 24893135]
10. Erlic Z, Rybicki L, Peczkowska M, et al. Clinical predictors and algorithm for the genetic diagnosis of pheochromocytoma patients. *Clin Cancer Res.* 2009; 15:6378–6385. [PubMed: 19825962]
11. Aufforth RD, Ramakant P, Sadowski SM, et al. Pheochromocytoma Screening Initiation and Frequency in von Hippel-Lindau Syndrome. *J Clin Endocrinol Metab.* 2015; 100:4498–4504. [PubMed: 26451910]
12. Hermesen MA, Sevilla MA, Llorente JL, et al. Relevance of germline mutation screening in both familial and sporadic head and neck paraganglioma for early diagnosis and clinical management. *Cell Oncol.* 2010; 32:275–283. [PubMed: 20208144]
13. Rinaldo A, Myssiorek D, Devaney KO, et al. Which paragangliomas of the head and neck have a higher rate of malignancy? *Oral Oncol.* 2004; 40:458–460. [PubMed: 15006616]

14. Tsang VH, Tacon LJ, Learoyd DL, et al. Pheochromocytomas in Multiple Endocrine Neoplasia Type 2. *Recent Results Cancer Res.* 2015; 204:157–178. [PubMed: 26494388]
15. Fishbein L. Pheochromocytoma and Paraganglioma: Genetics, Diagnosis, and Treatment. *Hematol Oncol Clin North Am.* 2016; 30:135–150. [PubMed: 26614373]
16. Zografos GN, Vasiliadis GK, Zagouri F, et al. Pheochromocytoma associated with neurofibromatosis type 1: concepts and current trends. *World J Surg Oncol.* 2010; 8:14. [PubMed: 20219130]
17. Bausch B, Borozdin W, Neumann HP. Clinical and genetic characteristics of patients with neurofibromatosis type 1 and pheochromocytoma. *N Engl J Med.* 2006; 354:2729–2731. [PubMed: 16790714]
18. Comino-Mendez I, Gracia-Aznarez FJ, Schiavi F, et al. Exome sequencing identifies MAX mutations as a cause of hereditary pheochromocytoma. *Nat Genet.* 2011; 43:663–667. [PubMed: 21685915]
19. Burnichon N, Cascon A, Schiavi F, et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. *Clin Cancer Res.* 2012; 18:2828–2837. [PubMed: 22452945]
20. Hammond PJ, Murphy D, Carachi R, et al. Childhood phaeochromocytoma and paraganglioma: 100% incidence of genetic mutations and 100% survival. *J Pediatr Surg.* 2010; 45:383–386. [PubMed: 20152357]
21. Mazzaglia PJ. Hereditary pheochromocytoma and paraganglioma. *J Surg Oncol.* 2012; 106:580–585. [PubMed: 22648936]
22. Timmers HJ, Chen CC, Carrasquillo JA, et al. Comparison of 18F-fluoro-L-DOPA, 18F-fluoro-deoxyglucose, and 18F-fluorodopamine PET and 123I-MIBG scintigraphy in the localization of pheochromocytoma and paraganglioma. *J Clin Endocrinol Metab.* 2009; 94:4757–4767. [PubMed: 19864450]
23. Fikri AS, Kroiss A, Ahmad AZ, et al. Localization and prediction of malignant potential in recurrent pheochromocytoma/paraganglioma (PCC/PGL) using 18F-FDG PET/CT. *Acta Radiol.* 2014; 55:631–640. [PubMed: 24037430]

Figure 1.
Frequency of distribution by age category of pheochromocytoma (PC) and paraganglioma (PGL).

Table 1

Demographics, clinical and genetic features

Variable	Mean $\pm$ SD, Number (%)
Age at presentation	13.9 $\pm$ 5.03 years
Gender, n (%)	
Male	30 (54.5)
Female	25 (45.5)
Germline Mutations, n (%)	
<i>VHL</i>	21 (38.2)
<i>SDHB</i>	13 (23.6)
<i>SDHD</i>	4 (7.3)
<i>SDHA</i>	1 (1.8)
<i>RET</i>	3 (5.5)
<i>NFI</i>	1 (1.8)
<i>MAX</i>	1 (1.8)
No known germline mutation	11 (20)
Tumor Location, n (%)	
Adrenal	37 (67)
Extra-adrenal abdominal	12 (21)
Extra-adrenal head and neck	6 (10.9)
Extra-adrenal thoracic [†]	2 (3)
Number of tumors, n (%)	
Solitary	41 (74.5)
Multiple	14 (25.5)
Malignancy, n (%)	
Benign	47 (85.6)
Malignant	9 (16.4)
Recurrence, n (%)	
Recurrence in remnant adrenal gland [‡]	6 (10.9)
Recurrence in contralateral adrenal gland	11 (20)
Recurrence at different anatomic site (not metastatic) [§]	16 (29)
Initial Presentation, n (%)	
<i>Signs and symptoms</i>	
Screening because of family history	22 (40)
Hypertension	17 (30.9)
Headaches	2 (3.6)
Neck mass	3 (5.5)
Thyroid nodule	2 (3.6)

Variable	Mean $\pm$ SD, Number (%)
Clinical manifestations (café-au lait spots)	1 (1.8)
Other (dysphagia, abdominal pain, polycythemia, anemia)	4 (7.3)
Unknown	4 (7.3)
Biochemical Evaluation, n(%) ^{//}	
Plasma fractionated metanephrines (ref 12–61 mcg/24 hr), n=53	
Normal	45 (85)
Elevated	8 (15)
Plasma fractionated normetanephrines (ref 18–112 pg/mL), n=53	
Normal	16 (30.2)
Elevated	37 (69.8)
24 hr urine metanephrines (ref 69–221 mcg/24 hr), n=43	
Normal	40 (93)
Elevated	3 (7)
24 hr urine normetanephrines (ref 29–145 mcg/24 hrs), n=43	
Normal	28 (65.1)
Elevated	15 (34.9)
Total 24 hr urine metanephrines (ref 57–210 mcg/24 hr), n=49	
Normal	31 (63.3)
Elevated	18 (36.7)
Plasma dopamine (ref 3–46 pg/mL), n=45	
Normal	28 (62.2)
Elevated	17 (37.7)
24 hr urine dopamine (ref 65–400 mcg/24 hrs), n=44	
Normal	38 (86.4)
Elevated	6 (13.6)

[†]Two patients with previous PC/PGL resections presented with thoracic PGLs on follow-up

[‡]One patient with positive margins

[§]Patients had more than one recurrence

^{//}Records not available for all patients

Table 2

Summary of mutations by anatomic tumor location

Tumor type	Number	VHL	SDHB	SDHD/A	RET	MAX	NF1	No known germline mutation
PC	37	20	3	2	3	1	1	7
Solitary	18	5	3	1	2	1	1	5
Bilateral	19	15	-	1	1	-	-	2
PGL	18	1	10	3	-	-	-	4
A-PGL	12	1	8	-	-	-	-	3
HN-PGL	6	-	2	3	-	-	-	1
T-PGL	2 [*]	1 [*]	1 [*]	-	-	-	-	-
Total	55	21	13	5	3	1	1	11

PC=pheochromocytoma; PGL=paraganglioma; A-PGL=abdominal; HN-PGL=head and neck; T-PGL=thoracic pgl

^{*}Two patients with previous PC/PGL resections presented with thoracic PGLs during follow-up

Table 3

Number of tumors detected by preoperative imaging studies in patients with PC/PGL

Imaging	Anatomic Location (n ₁)			
	Total	Adrenal	Abdominal PGL	Head & neck/ Thoracic PGL
	71	36	28	7
CT (n=45)	57	35	15	7
MRI (n=37)	48	25	17	6
¹⁸F-FDG PET/CT (n=30)	45	19	20	6
I-¹²³MIBG (n=26)	26	20	6	*
¹⁸F-FDOPA PET/CT (n=10)	21	6	13	2
¹⁸F-FDA PET/CT (n=6)	14	3	11	*
⁶⁸Ga-DOTATATE PET/CT (n=4)	6	4	2	*

* Imaging was not performed in patient(s)

n = number of radiological studies performed

n₁ = number of histologically confirmed lesions

Table 4

Detection rate of preoperative imaging studies in patients with PC/PGL

Imaging Modality	Detection Rate %				
	Abdominal PC and PGL	PC	Abdominal PGL	Head & neck/ Thoracic PGL	Skeletal Metastasis
CT	87.8	100	68.2	100	100
MRI	84	92.6	74	100	100
¹⁸ F-FDG PET/CT	90.7	86.4	95.2	100	100
¹¹²³ MIBG	81.2	90.9	60	*	33.3
¹⁸ F-FDOPA PET/CT	86.4	100	81.3	100	100
¹⁸ F-FDA PET/CT	93.3	100	91.6	*	100
⁶⁸ Ga-DOTATATE PET/CT	60	100	33.3	*	*

* Imaging was not performed