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Preoperative genetic testing in pheochromocytomas and paragangliomas influences the surgical approach and the extent of adrenal surgery

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Background. Our knowledge of the susceptibility genes for pheochromocytomas/paragangliomas has increased; however, data on its impact on surgical decision-making has not been described. The aim of this study was to determine the effect of routine preoperative genetic testing on the operative intervention in patients with pheochromocytomas/paragangliomas.
Methods. One-hundred-eight patients diagnosed with pheochromocytomas/paragangliomas who underwent 118 operations had preoperative genetic testing for 9 known pheochromocytoma/paraganglioma susceptibility genes. A retrospective analysis of a prospective database was performed to evaluate clinical factors associated with the surgical approach selected and the outcome of the surgical intervention.
Results. In 51 patients (47%), a germline mutation was detected and one-third had no family history of pheochromocytoma/paraganglioma. In 77 operations (65%), it was the first operative intervention for the disease site (60 laparoscopic, 17 open), and 41 (35%) were reoperative interventions (36 open, 5 laparoscopic). For initial operations, variables associated with whether an open or laparoscopic approach was used were tumor size (P = .009) and presence of germline mutation (P = .042). Sixty-eight adrenal operations were performed (54 total, 14 cortical-sparing). Variables significantly associated with a cortical-sparing adrenalectomy being performed were the presence of germline mutation (P = .006) and tumor size (P = .013).
Conclusion. Preoperative knowledge of the germline mutation status affects the surgical approach and extent of adrenalectomy. (Surgery 2017;160:XXX-XXX.)

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Pheochromocytoma (PC) is a tumor that originates from chromaffin cells of the adrenal medulla, while paraganglioma (PGL) arises from the chromaffin cells of sympathetic and parasympathetic ganglia, as defined by the World Health Organization (WHO). PC/PGL is present in 0.1–0.6% of patients with hypertension and is found in 0.05% of patients during autopsy.[1] Most PCs/PGLs hypersecrete catecholamines and their metabolites, which may cause difficult-to-control hypertension, diabetes mellitus, and cardiovascular morbidity.[2] Patients may also present with an incidentally discovered mass or with vague symptoms, which include diaphoresis, headaches, palpitations, and anxiety.[1]

PC/PGL may be sporadic or inherited. Inherited PC/PGL syndromes include neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 2, von Hippel-Lindau syndrome (VHL), myc-associated factor X (MAX), and familial PC/PGL with succinate dehydrogenase mutations. There has been considerable progress made in our knowledge of the susceptibility genes that predispose to PCs/PGLs, and there are 12 well-known germline mutations related to these tumors. The germline mutations occur in the following genes: *RET*, *VHL*, *NF1*, *SDHA-D*, *MAX*, *FH, KIF1β, SDHAF2,* and *TMEM127*.[3] The frequency of germline mutation in patients with PC/PGL is up to 40% in patients of all ages and can be as high as 80% in the pediatric population.[4]

There is no data on preoperative genetic testing and its impact on the surgical treatment of PC/PGL. The aim of this study was to determine if routine preoperative genetic testing was associated with the type of operative intervention and the extent of adrenalectomy used in patients with PC/PGL and to determine the rate of clinically unknown inherited PC/PGL.

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Methods

One hundred eight patients diagnosed with PC/PGL underwent resection of their tumors at the National Institutes of Health Clinical Center between November 2009 and September 2016. After informed consent was obtained, all patients were enrolled in clinical protocols (NCT00004847, NCT01005654). The study was approved by the institutional review boards of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and the National Cancer Institute. Only patients with a histologic diagnosis of PC/PGL were included in the study. The operations were classified into first-time operations and reoperations. A reoperation was defined as having a previous operation at the same site as the newly diagnosed tumor. Preoperative genetic testing was performed for known PC/PGL susceptibility genes (*RET*, *VHL*, *NF1*, *SDHA-D*, *MAX*, and *FH*) in a Clinical Laboratory Improvement Amendments certified laboratory.

We performed a retrospective analysis of prospectively collected data on demographic characteristics (age, sex, and ethnicity/race), clinical data (body mass index, operative approach, operative duration, the extent of adrenalectomy, tumor size, and pathologic diagnosis), and genetic testing results, as well as laboratory data including preoperative and postoperative 24-hour urine and plasma dopamine, epinephrine, norepinephrine, free metanephrine, and free normetanephrine. Patients with laboratory values elevated to 2 times the upper limit of normal or higher were considered to have functional tumors. Biochemical remission was defined as a postoperative laboratory value <2 times the upper limit of normal in patients with a functional tumor on a preoperative evaluation.

Statistical analysis

Univariate analysis using Spearman's correlation coefficient, Student *t* test, and χ^2 tests and multivariate analysis using logistic regression were performed. We analyzed demographic characteristics, clinical factors, and genetic information to evaluate their impact on the surgical approach selected and the extent of adrenalectomy. Two-tailed *P* values were used and reported. IBM SPSS Statistics Data Editor (New York, NY) and Microsoft Excel (Redmond, WA) were used for statistical analyses.

Results

The demographic and clinical characteristics of the study cohort are summarized in Table I. One hundred eight patients underwent 118 operations. Eight patients underwent >1 operation. In 51 patients (47%), a germline mutation was detected. In 17 of the 51 patients (33%) with a germline mutation (1 *VHL*, 1 *FH*, 2 *RET*, 1 *SDHA*, and 11 *SDHB*) there was no family history of PC/PGL or family members with a positive genetic testing result.

In 76 operations (65%), it was the first operative intervention for the disease site, 60 of which were performed with a laparoscopic approach, and 17 with an open approach (Fig 1). Forty-one operations (35%) were reoperative interventions, 36 of which were open and 5 were laparoscopic. Twenty-five patients (17 no germline mutation, 5 *SDHB*, 1 *SDHA*, 1 *VHL*, and 1 *RET*) underwent an operation for metastatic disease. In patients with functional tumors, 79% of the operations resulted in biochemical remission. Factors associated with a higher risk of persistent/recurrent disease on biochemical testing were an open surgical approach ($P < .001$), presence of metastatic disease ($P < .001$), reoperations ($P < .001$), and male sex ($P < .05$), but not age, body mass index, and presence of germline mutation.

Table I
Demographic, clinical, and biochemical data in study cohort

Variables		108 patients
Median age, y (range)		42 (5–76)
Median BMI (range)		26.41 (14.08–45.13)
Sex (female/male)		60/48
Type of operation		
Initial videoscopic transabdominal/redo videoscopic transabdominal		58/2
Initial open/redo open		17/36
Initial videoscopic retroperitoneal/redo videoscopic retroperitoneal		2/3
Mean surgery duration (min; range)		209 (65–615)
Genetic mutation		
Present		51
Not present		57
Adrenalectomies		
Partial		14
Total		54
Functional status of tumor (≥2 times the upper limit of normal) at the time of the operation		
Functional		100
Nonfunctional		18*
Biochemical Remission (2 times upper limit of normal)		
Remission/No remission		80/17
No information available		21
Plasma biochemistries		
Preoperative values (normal range)	**Median**	**Range**
Dopamine (5–23)	18	0–3,112
Epinephrine (4–58)	27	0–2,418
Norepinephrine (84–794)	879.5	72–14,861
Metanephrine (12–61)	49	0–5,996
Normetanephrine (18–112)	493.5	16–23,350
Postoperative values	Median	Range
Dopamine	10	0–507
Epinephrine	6	0–185
Norepinephrine	260	89–3,338
Metanephrine	18	0–357
Normetanephrine	67.5	0–2,282
Urinary biochemistries		
Preoperative values	**Median**	**Range**
Dopamine (65–400)	289	20–9,704
Epinephrine (0–20)	6.65	0–789
Norepinephrine (15–80)	134	19–4,287
Metanephrine (0–261)	169	0–22,920
Normetanephrine (0–451)	1,617.5	155–31,175
Postoperative values	**Median**	**Range**
Dopamine	195	0–683
Epinephrine	2.5	0–51
Norepinephrine	41	4–1,837
Metanephrine	72	0–1,558
Normetanephrine	318	92–15,374

* Number >108 patients based on the number of operations.
BMI, body mass index.

Minimally invasive versus open surgical approaches for initial operative interventions

The demographic and clinical characteristics of 76 patients who underwent PC/PGL resection as their initial operation are summarized in Table II. A germline mutation in susceptibility genes was present in 39 patients. Twenty-nine patients with a germline mutation (8 *VHL*, 14 *RET*, 4 *SDHB*, 1 *NF1*, 1 *MAX*, and 1 *MEN1*) underwent minimally invasive surgery and 10 (7 *SDHB*, 1 *SDHA*, 1 *SDHD*, 1 *VHL*) underwent an open operation. The average tumor size in patients who underwent a minimally invasive approach was significantly smaller than those of patients who had an open surgery (3.9 vs 5.8 cm, $P < .01$). Clinical characteristics associated with whether an open or laparoscopic approach was used were tumor size ($P < .01$) and presence of germline mutation in known susceptibility genes ($P < .05$). Comparing patients with a germline mutation in *RET*, *VHL*, or *NF1* with the rest of the cohort undergoing an initial operation, patients with the aforementioned mutations were more likely to

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