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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Clinical Predictors of Malignancy in Patients with Pheochromocytoma and Paraganglioma

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ABSTRACT

Background and Purpose. Factors associated with malignancy in patients with pheochromocytoma (adrenal tumors, Pheo) and paraganglioma (extra-adrenal, PGL) are not well-defined and all patients require lifelong surveillance. The primary aim of our study was to determine genetic and clinical variables associated with malignancy in patients with Pheo/PGL.

Methods. Single institution retrospective review was performed of all patients who underwent surgery (1/95–1/15) for Pheo/PGL. Malignancy was defined as histology-confirmed distant metastasis, lymph nodal involvement, or tumor bed recurrence.

Results. A total of 157 Pheo/PGL patients (44 malignant, 113 benign) with mean follow-up of 87 months were included. Compared with patients with benign Pheo/PGL, patients with malignant Pheo/PGL were younger (median 42 vs 50 years, $p = 0.014$), had larger tumors (median 6.5 vs 4 cm, $p < 0.001$) and had PGL (63.6 vs 4.4%, $p < 0.001$). Genetic testing was performed in 60 patients and was positive in 38 (63%). Although positive genetic results were equally likely in malignant vs benign Pheo/PGL (76 vs 54%, $p = 0.1$), all 11 patients with germline *SDHB* mutations had malignant disease. In multivariable analysis, younger age, larger tumor size, and PGL were associated with malignancy ($p < 0.05$). Pheo patients with negative genetic testing and negative family history who developed metachronous metastases all had primary tumors ≥4 cm in size.

Conclusions. Patients who are young, have larger tumors, positive genetic testing (especially *SDHB*) or have PGL require long-term follow-up. Patients with negative genetic testing or family history and Pheo <4 cm have a lower risk of malignancy, and de-escalated long-term surveillance may be appropriate follow-up.

Pheochromocytoma (Pheo) refers to the chromaffin-cell tumors of the adrenal medulla, and paraganglioma (PGL) are the less common extra-adrenal chromaffin-cell tumors.[1,2] PGL mainly arise in the para-vertebral sympathetic ganglia of the thorax, abdomen, and pelvis, and less commonly in the parasympathetic ganglia of the head and neck.[1,2] Pheo also accounts for 4-8% of adrenal incidentalomas.[3] It is estimated that the prevalence of Pheo/PGL is somewhere between 1 in 6500 and 1 in 2500, with an estimated annual incidence of 500–1600 cases per year in United States.[1] Recent years have seen advances in the management of Pheo/PGL.[1–4] An improved understanding of the underlying genetic alterations associated with Pheo/PGL has revealed that up to one-third of patients may have a germline genetic mutation. The most commonly involved genes include *VHL, SDHx, RET,* and *NF1*.[2,5] Despite these advances, the distinction between benign and malignant Pheo/PGLs remains challenging.[3,6]

Malignancy can be seen in 2–26% of patients with apparently benign Pheo/PGL and can occur decades after initial diagnosis.[4,6] The presence of metastatic disease remains the only definitive criteria for malignancy based on World Health Organization (WHO) classification.[7] Histologic features which are one of the most useful prognostic factors in other solid tumors, have not been shown to

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reliably predict malignancy.[4] Thompson et al. performed a comprehensive analysis of 100 Pheos including 50 malignant tumors, and formulated the pheochromocytomas of the adrenal gland score (PASS) based on 12 histologic features such as diffuse growth, high cellularity, cellular monotony, tumor cell spindling, mitotic figures >3/10 HPF, atypical mitoses, profound nuclear pleomorphism and nuclear hyperchromasia.[8] However, many of the features are associated with inter- and intra-observer variability and therefore the PASS is difficult to replicate.[9] Similarly, imaging or biochemical characteristics have not been able to consistently differentiate malignant from benign Pheo/PGL.[4]

Recent studies have shown that some of the most useful clinical factors associated with malignancy are large size (>4–5 cm), and genetic features such as presence of *SDHB* germline mutations.[10–12] There are no clinical algorithms for follow-up of patients using these criteria, and given the limitations of histopathologic features to predict malignancy, long term follow-up is currently recommended for all patients.[3] We hypothesized that clinical and genetic features may allow clinicians to risk stratify patients, and lead to more precise surveillance strategies. The primary aim of this study was to determine the clinical and genetic factors which may be associated with malignancy in Pheo/PGL patients and to propose an algorithm for follow-up.

METHODS

The study is a retrospective review of consecutive patients who had surgery for Pheo/PGL (1/95–1/15). After institutional QA/QI approval, data were collected on clinical and pathology-related variables. Patients all had a histopathological and biochemically-confirmed diagnosis of Pheo/PGL. Given the long study interval, practice patterns varied over time. Patients were evaluated preoperatively with plasma free metanephrines or 24-h urinary fractionated metanephrines or both. Some patients had plasma free catecholamines or 24-h urinary fractionated catecholamines. Our usual approach for follow up is to obtain plasma or 24 h urinary fractionated metanephrines at ~1 and 6 months after resection, and then yearly plasma or 24 h fractionated metanephrines. Cross-sectional imaging (usually CT scan) is obtained at 6 months and subsequent imaging is based on symptoms, and the results of biochemical and genetic testing. Anatomic imaging is done routinely for patients with nonfunctional tumors.

Adrenal tumors were coded as Pheo and extra-adrenal location was coded as PGL.[2] Patients presenting with both adrenal and extra-adrenal tumor were coded as PGL. Positive family history was defined as Pheo/PGL in a first degree relative. Malignancy was defined as histology-confirmed distant metastasis, lymph node involvement, or tumor bed recurrence. Patients with recurrent, metachronous Pheo/PGL did not have malignancy. Genetic testing [2] has been routinely recommended for all Pheo/PGL patients within the last ~10 years and prior to that, patients were referred selectively based on family history, presence of multifocal disease, and/or young patient age. Depending on the testing modality available, genetic testing was performed using algorithmic testing and direct sequencing of the most likely affected gene or more recently, using a next generation sequencing gene panel, based on the discretion and assessment of the clinical geneticist. Positive genetic testing was defined as any gene mutation associated with a predisposition for Pheo/PGL regardless of benign vs malignant status.

Statistics

Continuous variables were summarized as means (±standard deviation) or medians (range). Chi squared test or Fisher's exact test were used for comparison of categorical variables and Mann–Whitney *U* test was used to compare continuous variables. Univariable and multivariable analyses were performed using logistic regression. Data were reported as odds ratios and 95% confidence interval (CI). Variables were introduced into the multivariable model to predict malignancy (referent—benign category) based on statistical significance and clinical relevance. All analyses were performed using STATA 14.1 (Statacorp, 4905 Lakeway Drive, College Station, Texas, US).

RESULTS

Patient characteristics

In total, 157 Pheo/PGL patients were included in the study (Table 1). Mean follow-up was 87 months (range 1–580). Median age at the time of initial diagnosis was 48 years (range 9–78). The majority (70.7%) of patients were symptomatic at the time of presentation and had hypertension, localized pain, episodic diaphoresis, and/or palpitations, and 13.8% (21/157) had a family history of Pheo/PGL. The median tumor size was 4.5 cm (range 1.2–25 cm) and 21% were PGL. Among patients with Pheo (adrenal tumors) 26.3% had an initial open resection and the remaining had laparoscopic resection. Malignancy was diagnosed in 44 patients (28%). Indicators of malignancy included distant metastasis in 34 patients and LN metastasis in 10 patients. Among three patients with tumor bed recurrence, two had concurrent distant metastasis and one had LN involvement. Patients with malignant Pheo/PGL were younger (median 42 vs 50 years, p 0.014), had larger

TABLE 1 Demographic characteristic of the study population ($N = 157$)

	All patients $N = 157$	Benign $N = 113$	Malignant $N = 44$	p Value[a]
Age (year), median (range)	48 (9–78)	50 (9–78)	42 (10–77)	**0.014**
Women, *n* (%)	89 (56.7)	66 (58.4)	23 (52.3)	0.486
Symptoms due to Pheo/PGL, *n* (%)	106 (70.7)	75 (67)	31 (81.6)	0.087
Family history, *n* (%)	21 (13.8)	12 (10.9)	9 (21.4)	0.093
Size (cm), median (range)	4.5 (1.2–25)	4 (1.2–16)	6.5 (2.2–25)	**<0.001**
Location, extra-adrenal, *n* (%)	33 (21)	5 (4.4)	28 (63.6)	**<0.001**
Positive genetic testing, *n* (%) ($N = 60$)	38 (63.3)	19 (54.3)	19 (76)	0.108

[a] Benign versus malignant

primary tumors (median 6.5 vs 4 cm, $p < 0.001$), and had PGL (63.6 vs 4.4%, $p < 0.001$) (Table 1). Among patients with Pheo, malignant tumors were more likely to undergo an initial open resection (open resection—malignant 78.6% vs benign 16.3%, $p < 0.001$).

Genetics

Germline genetic testing was performed in 60 Pheo/PGL patients and 38 (63.3%) were positive for mutations including *VHL* (13, 21.7%), *SDHB* (11, 18.3%), *NF1* (6, 10%), *RET* (5, 8.3%), and *SDHD* (3, 5%). Although positive genetic testing results were equally likely in malignant compared to benign Pheo/PGL (76 vs 54.3%, $p = 0.108$), all 11 patients with germline *SDHB* mutations had malignant disease ($p < 0.01$) while all 5 patients with *RET* mutations were benign (0.07) (Fig. 1).

Factors Associated with Malignancy

In the univariable logistic regression analysis, younger age, increasing size, extra-adrenal location and *SDHB/D* mutations each demonstrated a statistically significant association with malignancy (Table 2). For the multivariable analysis, only factors that were available for all patients, significant in univariable analysis, and/or clinically relevant were considered, and included the following covariates: age (continuous variable), known family history of Pheo/PGL, location (adrenal/extra-adrenal), and size (continuous variable). In the multivariable model, younger age, larger tumor size, and extra-adrenal location (e.g. PGL) were each found to be independently associated with malignancy (Table 2). When PGL patients are excluded, Pheo patients with negative genetic testing and family history who developed metachronous metastases all had primary tumors ≥4 cm in size. The model demonstrated an area under the receiver operator curve of 91.5% which signifies high accuracy of the model in predicting malignancy.

Outcomes

Among the 44 patients with malignancy, 25 (56.8%) had metachronous metastasis and the median time to recurrence was 68 months (95% CI 42.6–80.5 months, Fig. 2). The timing of malignant diagnosis could not be confirmed in one patient (2.3%). Median overall survival (OS) for patients with malignancy was 16.9 years (95% CI 9.1–20.6 years) while the median OS for patients with benign Pheo/PGL was not reached. OS at 5-, 10- and 15-year for patients with benign disease were 87.7, 74.4 and 68.2% vs. 77.4, 61.7 and 51.4% for patients with malignant disease, respectively.

Clinical Algorithm

Based on the above-described findings, we then sought to determine how the clinical factors in the multivariable model could be used to classify malignant and benign Pheo/PGL. Since the odds ratio associated with age was close to 1 and a clear cutoff point could not be determined, other factors with better discrimination were used in the clinical algorithm such as tumor location, family history and size. The presence of a known family history of a genetic predisposition syndrome was not significant in the multivariable model but was included in the algorithm assessment given its clinical relevance. Family history may help identify patients with familial Pheo/PGL but who not yet have an identified predisposition syndromes. Additionally, given its importance genetic testing was also included in the algorithm even though results were not available for all patients. Statistical significance and clinical relevance were both taken into consideration for clinical algorithm.

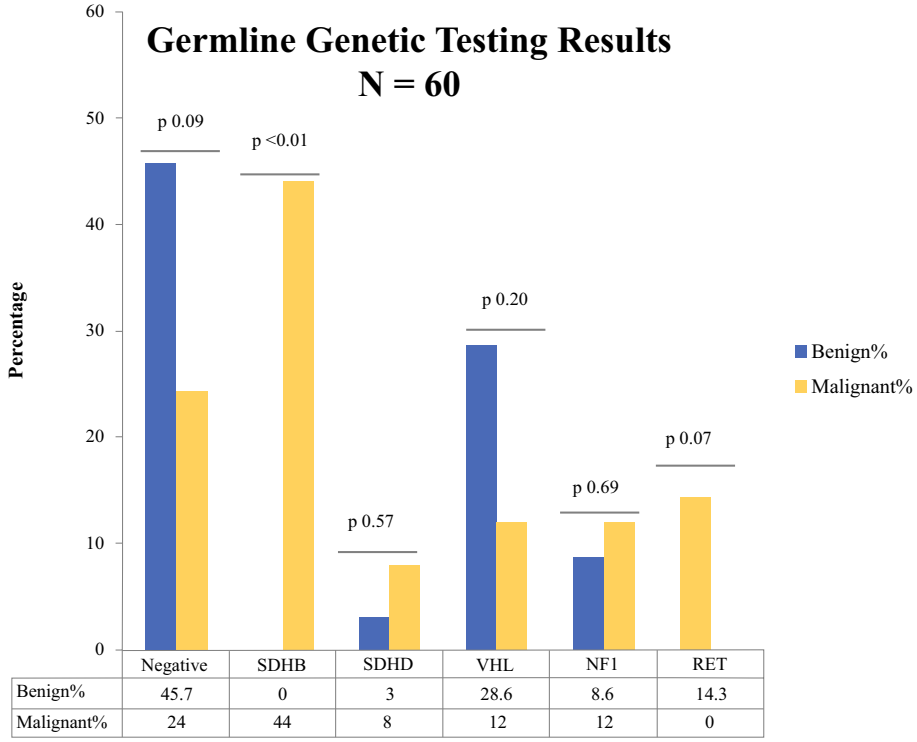


FIG. 1 Germline genetic testing results ($N = 60$) and comparison of various identified genetic mutations amongst malignant vs benign tumors. All patients with *SDHB* mutations had malignant tumors ($p < 0.01$)

TABLE 2 Univariable and multivariable analysis of factors associated with malignancy

	Univariable		
	OR	95% CI	*p* Value
Age	0.972	0.950–0.994	0.012
Women	0.78	0.387–1.570	0.486
Symptomatic	2.185	0.879–5.426	0.092
Positive family history	2.227	0.861–5.759	0.099
Size	1.274	1.110–1.464	0.001
Extra-adrenal (PGL)	37.8	12.749–112.069	<0.001
Positive genetic testing ($N = 60$)			
Neg		Ref	
SDHB/D	34.667	3.691–325.612	0.002
VHL	0.8	0.162–3.944	0.784
Others (NF/RET)	1	0.197–5.079	1
	Multivariable[a]		
	OR	95% CI	*p* Value
Age	0.964	0.930–0.999	**0.045**
Positive family history	1.382	0.275–6.948	0.694
Size	1.345	1.127–1.607	**0.001**
Extra-adrenal (PGL)	54.312	12.990–227.080	**<0.001**

[a] Genetic testing was not included in the multivariable model as results were only available for 60 patients

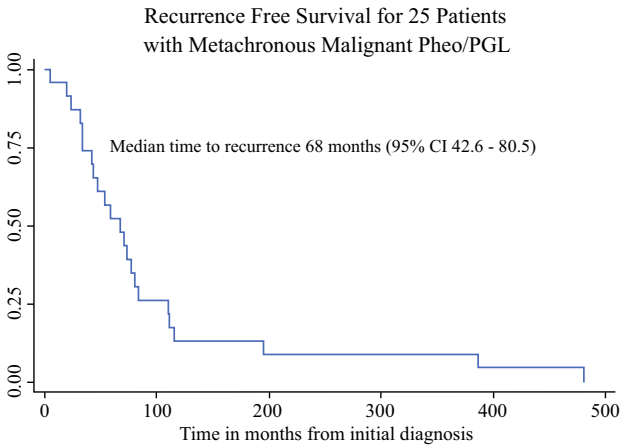


FIG. 2 Kaplan Meier graph depicting recurrence free survival for patients with metachronous malignant Pheo/PGL ($N = 25$). Median time to recurrence was 68 months (95% confidence interval 42.6–80.5 months)

We determined that when location, family history, genetic testing results, and size >4 cm were used sequentially with equal value assigned to each variable, there was 100% sensitivity in identifying all malignant patients. After stratifying the malignant tumors by the sequential criteria of location (extra adrenal—yes), family history (yes) and genetic testing (positive for any gene), the remaining tumors were all >4 cm in size (4.5–9 cm). We used the acronym *EPoGS* to represent the order in which the four clinical criteria for malignancy should be considered—1. Location—Extra-adrenal 2. Positive Family history 3. Genetic testing results and 4. Size >4 cm. Figure 3a provides the details of classification of the two study cohorts based on the EPoGS criteria. Based on the results depicted in Fig. 3a, we proposed a follow-up algorithm for patients with Pheo/PGL (Fig. 3b).

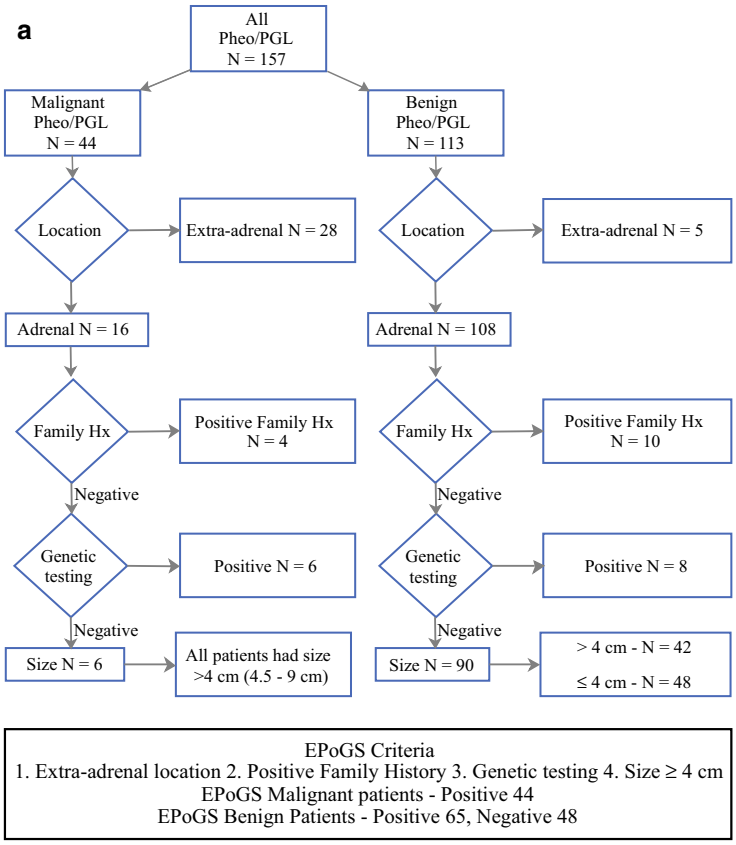
DISCUSSION

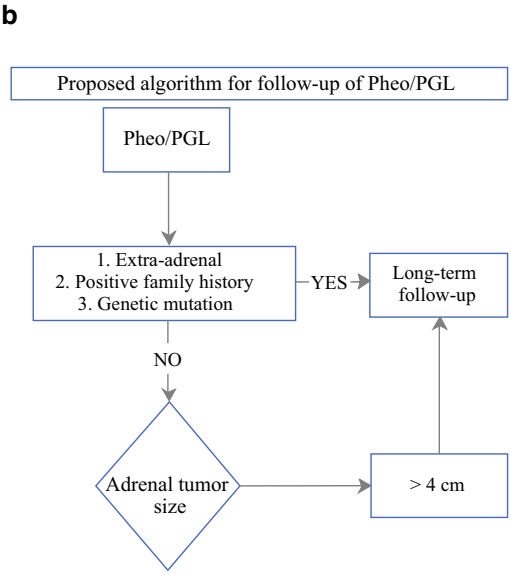
Malignancy in patients with Pheo/PGL is particularly difficult to predict and may present decades after initial diagnosis. In addition, although histopathologic factors may be helpful to identify Pheo/PGL with high malignant potential, there is significant inter- and intra-observer variability limiting routine use for clinical prognostication.[9] Given this challenge, extended long-term follow-up is recommended for all patients.[3] Recent studies have identified larger tumor size and *SDHB* mutation as factors predicting an increased risk of malignancy.[10–12] Others have suggested young age and extra-adrenal location are risk factors for malignancy as well.[2] No previous study has placed these variables together into context for routine clinical practice and follow-up. Our current study was undertaken with the aim of identifying clinical and genetic information that can be used to identify patients at risk for malignancy. This will ideally identify a subset of patients who may be at low risk for malignancy and be candidates for de-escalated follow-up.

In this large series we observed that all tumors with *SDHB* mutations were malignant although others have reported that not all SDHB positive Pheo/PGL are malignant.[11–13] Additional clinical factors such as younger age, positive family history, tumor size and extra-adrenal location were also found to be independently associated with malignancy. An affirmative to any of the 4 EPoGS criteria when queried sequentially (Location (Extra-adrenal—yes or no) → positive family history (yes or no) → genetic testing positive (yes or no) → size >4 cm) was associated with malignancy. The use of the EPoGS criteria had a sensitivity of 100% and a specificity of 42.5% for predicting malignancy. We therefore recommend that such patients should definitely undergo biochemical and/or imaging surveillance. Patients with small adrenal tumors (e.g. Pheo) ≤4 cm may be selected for de-escalated long-term surveillance as none had malignancy after a long mean follow-up of 7.3 years for our cohort thus far.

Our results are similar to those of Assadipour et al. who compared clinical, genetic and pathologic features of 35 sporadic and 49 *SDHB* mutated Pheo/PGL patients.[11] They reported that Ki67 and mitotic index were not associated with metastases, however tumor size and *SDHB* mutation were independent risk factors for local recurrence and metastasis. Larger tumor size (>4.5 cm) and *SDHB* mutation have also been reported by others as risk factor for recurrence and malignant behavior.[10,12,14] Similarly, it has been shown that young age is associated with increased incidence of *SDHB* and *VHL* germline mutations and extra-adrenal location.[15,16] The findings of the current study are thus in accord with previous studies consistently suggesting that age, family history, extra-adrenal location and germline testing results can be used to identify patients with malignant Pheo/PGL and this replicable clinical information can be used to risk stratify patients for follow-up. But to date, no clinical algorithm has been specifically devised taking these factors into account.

Recent collaborative efforts in Japan have led to the GAPP (Grading for Adrenal Pheochromocytoma and Paraganglioma) scoring system to predict malignant behavior.[17] GAPP criteria include six variables: histological pattern, cellularity, comedo-type necrosis, capsular/vascular invasion, Ki67 labelling index and catecholamine type and the maximum score is 10. These authors reported that the mean GAPP scores of non-metastatic vs metastatic tumors were 2.08 versus 5.33 ($p < 0.001$). However, germline genetic testing results were not analyzed as these were not available during the study period. Additionally, distribution of benign vs





EPoGS Criteria	Malignant	Benign
Pos	46 (TP)	65 (FP)
Neg	0 (FN)	46 (TN)

Test results (95% CI)	
Sensitivity	100% (91.96 - 100%)
Specificity	42.5% (32.2 - 52.1%)

FIG. 3 **a** EPoGS criteria including extra-adrenal location, positive family history, genetic testing and size >4 cm demonstrated a sensitivity of 100% and specificity of 42.5% for malignancy. **b** Proposed clinical algorithm for follow-up of patients with pheochromocytoma and paraganglioma

malignant tumors and individual GAPP scores were not reported. Among patients with loss of SDHB by immunohistochemical staining ($n = 13$), 4 patients with malignant behavior had a GAPP score of <6. The authors did not specifically assess the inter- and intra-observer variability of GAPP criteria which should be further investigated.

The proposed EPoGS criteria were deliberately designed to identify all patients with malignant Pheo/PGL and thus the specificity was low at 42.5%. However, if used clinically, ~40% of Pheo patients would likely have benefited from de-escalated surveillance. It is possible that additional pathologic criteria would be helpful to further risk stratify the 47 patients who had benign PGL and Pheo >4 cm. We did not observe any patients with *RET* mutations who had malignant disease and we also did not retest the 37% of patients who had initial negative genetic testing. There have been several germline mutations that have now been associated with an inherited predisposition to Pheo/PGL such as *MAX*, *TMEM127*, and additional *SDH* variants. Furthermore, currently available next generation sequencing technology has allowed for more cost-effective genetic screening that can be offered after appropriate counseling to all Pheo/PGL patients. Genetic testing can help identify 1st degree relatives at risk for Pheo/PGL and if a predisposition syndrome is identified, then screening for other related manifestations can be performed. As we (and others) have demonstrated, genetic testing also provides helpful Pheo/PGL-specific prognostic information particularly if comprehensive gene testing is negative.[2] It is our practice to recommend testing to all Pheo/PGL patients even in follow-up if they have not had it done previously, and refer all patients for genetic counseling. It is then at the patient's discretion whether to pursue such testing. As our experience with other genetic

predisposition syndromes increases, we anticipate that further risk stratification will be possible.

Our study is a single institutional retrospective series and there are associated limitations including selection and referral bias. Not all patients underwent comprehensive genetic testing and thus we could not include this variable in multivariable analysis. We had large sample size and long mean follow-up of 87 months which adds to the strength of the study, but it is possible that with further follow-up, additional patients with metastatic Pheo/PGL will be diagnosed who were not initially captured. Also, we coded synchronous pheo/PGL tumors as PGL which could have favored our results in achieving high sensitivity. However, given the high risk of malignancy associated with extra-adrenal location, patients with concurrent Pheo and PGL should be treated similar to PGL alone. We did not compare the EPoGS criteria with PASS score as PASS score is not reported at our institution given the limited broad-based clinical utility. We observed a median recurrence free survival that was relatively long at 68 months suggesting that the metastases were not a result of incomplete tumor resection. The current study is the first to compile the clinical and genetic factors into a follow-up algorithm for these patients. Although the study lacks prospective, external validation, factors such as extra-adrenal location, larger size and genetic testing results have been previously reported to be associated with malignant behavior in Pheo/PGL patients by others and support the findings of the current study.

In conclusion, our study confirms that *SDHB* mutations are associated with high risk of malignancy and shows in multivariable analysis that other replicable clinical criteria such as extra-adrenal location (e.g. PGL), positive family history, any positive genetic testing and larger adrenal (>4 cm) tumor size can help identify patients who are at risk of malignancy (sensitivity 100%). These criteria can be used to identify patients who require long term follow-up.

DISCLOSURE There are no conflicts of interest involving the work under consideration for publication.

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