Clinical Risk Factors for Malignancy and Overall Survival in Patients with Pheochromocytomas and Sympathetic Paragangliomas: Primary Tumor Size and Primary Tumor Location as Prognostic Indicators

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Context: Pheochromocytomas and sympathetic paragangliomas are rare neuroendocrine tumors for which no precise histological or molecular markers have been identified to differentiate benign from malignant tumors.

Objective: The aim was to determine whether primary tumor location and size are associated with malignancy and decreased survival.

Design and Setting: We performed a retrospective chart review of patients with either pheochromocytoma or sympathetic paraganglioma.

Patients: The study group comprised 371 patients.

Main Outcome Measures: Overall survival and disease-specific survival were analyzed according to tumor size and location.

Results: Sixty percent of patients with sympathetic paragangliomas and 25% of patients with pheochromocytomas had metastatic disease. Metastasis was more commonly associated with primary tumors located in the mediastinum (69%) and the infradiaphragmatic paraaortic area, including the organ of Zuckerkandl (66%). The primary tumor was larger in patients with metastases than in patients without metastatic disease ($P < 0.0001$). Patients with sympathetic paragangliomas had a shorter overall survival than patients with pheochromocytomas ($P < 0.0001$); increased tumor size was associated with shorter overall survival ($P < 0.001$). Patients with sympathetic paragangliomas were twice as likely to die of disease than patients with pheochromocytomas (hazard ratio = 1.93; 95% confidence interval = 1.20–3.12; $P = 0.007$). As per multivariate analysis, the location of the primary tumor was a stronger predictor of metastases than was the size of the primary tumor.

Conclusions: The size and location of the primary tumor were significant clinical risk factors for metastasis and decreased overall survival duration. These findings delineate the follow-up and treatment for these tumors. **(*J Clin Endocrinol Metab* 96: 717–725, 2011)**

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Abbreviations: CI, Confidence interval; HR, hazard ratio; PGL, paraganglioma; PHEO, pheochromocytoma; sPGL, sympathetic PGL.

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine tumors. According to the Pheochromocytoma and Paraganglioma Alliance, approximately 55,000 new PHEO and PGL cases are expected each year worldwide. Most of these tumors are benign. Although the rate of malignancy has long been cited as 10% (1), others have estimated that it may be as high as 26% (2). In contrast to many other cancers, malignant PHEOs and PGLs lack histological or molecular markers that reliably distinguish them from benign tumors (1). The World Health Organization classification lists the presence of metastases, not local invasion, as the only accepted criterion for a diagnosis of malignant PHEO or PGL (3). Many malignant tumors may be initially classified as benign, with no follow-up after surgical resection of the primary tumor. Unfortunately, some of these cases may later present with widely metastatic disease for which surgery is no longer an option and chemotherapy may have variable efficacy. The 5-yr overall survival of patients with unresectable metastases is 40–72% (4, 5). Therefore, there is a need to identify clinical predictors of metastasis to better guide the treatment and follow-up of patients with these tumors.

In the past decade, researchers have made major advances in understanding the genetics and carcinogenesis of these tumors. It is now recognized that many PHEOs/PGLs occur as a consequence of deregulation in intracellular oxygen metabolism (6). Apart from the well-described familial syndromes associated with PHEO and PGL, such as multiple endocrine neoplasia type 2, neurofibromatosis type 1, and von Hippel-Lindau disease (7), inactivating germline mutations of the mitochondrial succinate dehydrogenase complex II subunits B, C, and D have also been described in PGL syndrome types 4, 3, and 1, respectively (8–10). Recently, germline mutations in the *SDHAF2* (PGL syndrome type 2) (11, 12), the *SDHA*, and the *TMEM127* genes have been described in association with PHEO/PGLs (13, 14). Mutations in the *SDHB* gene are the mutations most frequently associated with metastatic PHEO and PGL (2, 15–17). Although a causal link for the association has not been established yet, it is clear that mutations in the *SDHB* gene predict tumor aggressiveness and poor survival in PHEOs/PGLs (18). However, a substantial number of patients with metastatic PHEO or PGL (≥50%) do not carry the *SDHB* germline mutations (19).

Small series and case reports have suggested that the size and location of the primary tumor may be clinical predictors of aggressiveness in PHEOs/PGLs. For instance, metastases are rare in head and neck parasympathetic PGL (20), and large primary tumors have been frequently associated with metastases. Thus, we hypothesized that the size and location of the primary tumor at diagnosis are risk factors for metastases and therefore are associated with a reduced overall survival in patients with PHEO or sympathetic PGL (sPGL). The results of this analysis could help guide the aggressiveness of treatment and follow-up of patients with these tumors.

Subjects and Methods

Subjects

After obtaining approval from The University of Texas MD Anderson Cancer Center institutional review board, we searched the MD Anderson tumor registry and identified the medical records of 496 patients diagnosed with PHEO or PGL between 1960 and December 2009. We created a large database using Microsoft SQL Server (version 2008; Microsoft Corporation, Redmond, WA) and Microsoft Office (version 2007; Microsoft Corporation). We included 96 variables with demographic, clinical, laboratory, imaging, pathology, and treatment information. Primary tumor location and size and metastases were verified by pathology, surgical, and/or radiographic reports. Overall survival and disease-specific survival were analyzed according to tumor size and location. Because PGLs of the head and neck are usually non-hormone-producing parasympathetic tumors, patients with these tumors were excluded from this study. Patients whose diagnosis could not be confirmed by biochemical, radiographic, and/or histopathological studies in the record were also excluded.

We defined a PHEO as a chromaffin tumor originating in the adrenal medulla and sPGL as a chromaffin tumor originating in the sympathetic portion of the autonomic nervous system paraganglia outside the adrenal medulla. sPGLs were categorized according to the location of the primary tumor. The five types of sPGLs identified were: mediastinum, organ of Zuckerkandl, infradiaphragmatic paraaortic (other than the organ of Zuckerkandl), bladder, and other (*i.e.* peripancreatic, perirenal, *etc.*). For patients with multiple PHEOs and/or sPGLs, data were counted once, and the analysis was based on the clinical features of the largest tumor.

We defined metastatic disease as the presence of tumor in anatomical sites where chromaffin tissue is not normally present, such as the bone, liver, and lungs. Patients with metastases were subdivided into two groups: those who had metastatic disease at the time of diagnosis or within 6 months of diagnosis (synchronous metastases), and those who developed metastatic disease 6 months or more after diagnosis and resection of the primary tumor (metachronous metastases).

Statistical analyses

Descriptive statistics were used to provide a summary of the data. Frequency and percentages were reported for categorical variables; and summary statistics, including mean, SD, median, and range, were computed for continuous outcomes. We used the χ^2 test to compare categorical variables between patient subgroups. For continuous variables, we used the Wilcoxon rank sum test to evaluate differences in distribution between patient subgroups. We used the Kaplan-Meier method to estimate overall survival and the log-rank test to compare overall survival between patient subgroups; overall survival was defined as the

TABLE 1. Patient demographics

Patient demographics	PHEO	sPGL	*P* value	Total
Overall	267 (72%)	104 (28%)		371 (100%)
Age (yr)[a]	41 (6-83)	41 (5-77)	0.497[b]	41 (5-83)
Sex				
Male	123 (46.1%)	62 (59.6%)	0.019[c]	185 (49.9%)
Female	144 (53.9%)	42 (40.4%)		186 (50.1%)
Race				
White	205 (76.8%)	66 (63.5%)	0.013[c]	271 (73.0%)
Hispanic	29 (10.8%)	13 (12.5%)		42 (11.3%)
African-American	21 (7.9%)	20 (19.2%)		41 (11.0%)
Other	12 (4.5%)	5 (4.8%)		17 (4.6%)
Tumor size (cm)[a,d]	5.2 (0.4-21)	7 (1-24)	0.002[b]	6 (0.4-24)

[a] Data represent median (minimum–maximum).

[b] *P* value based on a Wilcoxon rank sum test.

[c] *P* value based on a χ^2 test.

[d] Based on 290 patients with complete data (214 pheochromocytoma; 76 paraganglioma).

time from the date of diagnosis of the primary tumor to the date of death or date of last follow-up for patients remaining alive. Univariate and multivariate Cox proportional hazards regression models were evaluated to assess the association of clinical factors with overall survival. All tests were two-sided, and *P* values less than 0.05 were considered statistically significant. All analyses were conducted using SAS (version 9.1; SAS Institute, Cary, NC) and S-plus 8.0 (TIBCO Software Inc., Palo Alto, CA).

Results

Patient demographics

After exclusions, the study group comprised 371 patients. Of these, 267 had PHEOs, and 104 had sPGLs. The median patient age at diagnosis was 41 yr (range, 5–83 yr), regardless of tumor type. This cohort included 185 males and 186 females. Males had fewer PHEOs (46.1%) than sPGLs (59.6%; $P = 0.019$). The distribution of tumor types by race was similar to overall distribution with the following exceptions: African-Americans had more sPGLs (19.2%) than PHEOs (7.9%), and whites had fewer sPGLs (63.5%) than PHEOs (76.8%; $P = 0.013$) (Table 1).

Tumor size

Primary tumor size was available in 290 patients. The size was determined by pathology, radiology, and surgical reports in 242 (83.5%), 41 (14.1%), and seven (2.4%) patients, respectively.

Computerized tomography became available in our institution in 1976. Of the 371 patients, 27 (7.2%) were diagnosed with PHEO/sPGL before 1976. Nine had metastases. It is then possible that a few patients with metastatic disease were missed.

Disease status by tumor type and location

Of the 267 patients with PHEOs, 68 patients (25.5%) had metastases, and 37 of them had metachronous metastases. Of the 104 patients with sPGLs, 63 patients (60.6%) had metastases, 27 of whom had metachronous metastases. The odds of metastases were nearly 4.5 times higher for patients with sPGLs than for patients with PHEOs [odds ratio = 4.5; 95% confidence interval (CI) = 2.8–7.3; $P < 0.001$]. In sPGL cases, incidence of metastasis was higher in patients with primary tumors located within the mediastinum (69%) or in the infradiaphragmatic paraaortic area, including the organ of Zuckerkandl (66%). Twenty-one patients had primary tumors located within the organ of Zuckerkandl, fourteen of whom had metastases (Table 2).

Overall survival by tumor type

The median follow-up time for the censored observations was 5.8 yr (range, 0.01–57.3 yr). Four patients with PHEOs whose tumors were diagnosed at autopsy were excluded from the overall survival analysis. When analyzing the overall survival rates of the remaining 263 patients with PHEOs and the 104 patients with sPGLs, we found that overall survival was 20.69 yr (95% CI = 17.04–30.80) for patients with PHEOs and 9.45 yr (95% CI = 6.53–16.80; log-rank test, $P < 0.0001$) for patients with sPGLs (Fig. 1A). Although patients with sPGLs exhibited a worse median survival than patients with PHEOs, the

TABLE 2. Location of sPGLs based on the presence of metastases

sPGL location	Nonmetastatic	Metastatic	Total
Infradiaphragmatic paraaortic	16 (34%)	31 (65.9%)	47
Organ of Zuckerkandl	7 (33.3%)	14 (66.6%)	21
Mediastinum	4 (30.7%)	9 (69.2%)	13
Bladder	5 (55.5%)	4 (44.4%)	9
Other	9 (64.2%)	5 (35.7%)	14

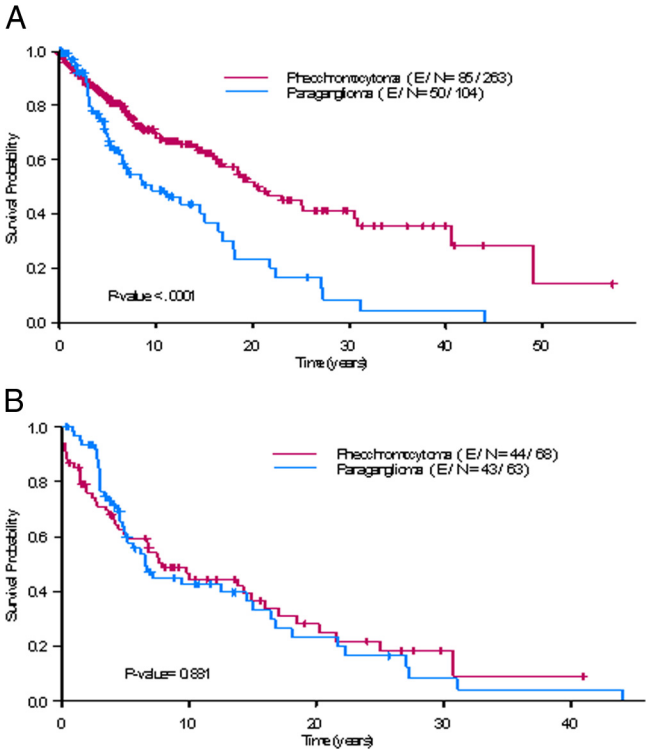

FIG. 1. A, Overall survival in patients with PHEOs and sPGLs. Four patients with PHEOs whose tumors were diagnosed at autopsy were excluded from the overall survival analysis. B, Overall survival in patients with metastatic PHEOs and sPGLs. E/N, number of events/total number of patients.

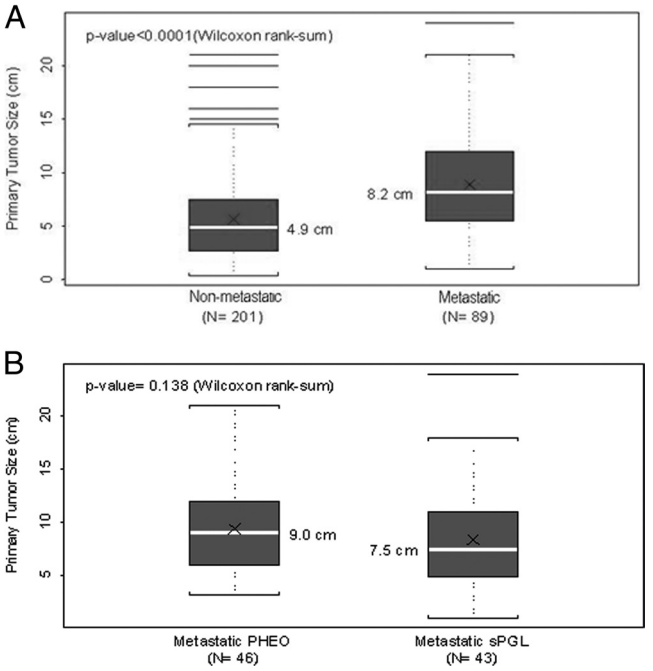

FIG. 2. A, Primary tumor size in patients with metastatic and nonmetastatic tumors. B, Primary tumor size in metastatic PHEOs and sPGLs.

survival rates of patients with metastatic disease were similar between the two tumor types (log-rank test, $P = 0.881$) (Fig. 1B).

Tumor size by disease status

The primary tumor size was available for analysis in 290 patients. Of these, 201 did not have metastases, and 89 had metastases. The primary tumor size was larger in patients with metastatic PHEO and sPGL than in patients with nonmetastatic disease. Regardless of tumor location, the median primary tumor size was 8.2 cm for tumors associated with metastases. The median primary tumor size was 4.9 cm for tumors not associated with metastases (Wilcoxon rank sum test, $P < 0.0001$) (Fig. 2A). There was no difference in median tumor size between metastatic PHEOs and metastatic sPGLs (median, 9.0 *vs.* 7.5 cm; $P = 0.138$) (Fig. 2B). Surprisingly, 16% of patients (14 of 89 patients with complete tumor size data) with metastatic disease had primary tumors smaller than 5 cm. Of these, 11 patients (78.5%) had sPGLs, including synchronous lymph node metastatic disease (n = 5), synchronous metastatic disease to the liver (n = 1), synchronous metastasis to the aortic arch (n = 1), metachronous metastases to the bone (n = 3), and metachronous metastases to the breast (n = 1). Three of the 14 patients (21.4%) had PHEOs, two of them had synchronous metastases to the liver, and one had synchronous metastases to lymph nodes.

Tumor size and overall survival rates

The median survival time for patients with tumors 5 cm or larger was 15.0 yr (95% CI = 7.6–25.1). The median survival time for patients with tumors smaller than 5 cm was 18.5 yr (95% CI = 16.5–NA; log-rank test, $P = 0.009$).

Hazard ratio (HR) for death: Cox proportional hazards regression models

In the univariate analysis, increased tumor size was significantly associated with worse overall survival (HR = 1.11; 95% CI = 1.06–1.15; $P < 0.0001$). Tumor size remained significant in the multivariate model (HR = 1.08; 95% CI = 1.04–1.13; $P = 0.0003$) while adjusting for age, gender, and tumor location. Patients with sPGLs had two times higher risk of death (HR = 2.03; 95% CI = 1.43–2.89; $P < 0.0001$) than patients with PHEOs. Tumor type (*i.e.* sPGL or PHEO) also remained significant in the multivariate model with a HR of 1.93 (95% CI = 1.20–3.12; $P = 0.0003$; Table 3). A separate analysis in patients with no metastatic PHEOs at diagnosis showed similar results (Table 4).

Frequency of synchronous *vs.* metachronous metastases

Fifty-one percent of the patients with metastatic disease had synchronous metastases, and 49% had metachronous

TABLE 3. Cox proportional hazards regression model for risk of death overall survival

Covariates	Univariate analysis				Multivariate analysis			
	No. of patients	No. of deaths	HR (95% CI)	*P* value	No. of patients	No. of deaths	HR (95% CI)	*P* value
Age (yr)	367	135	1.03 (1.02-1.04)	<0.0001	287	86	1.02 (1.01-1.04)	0.004
Gender								
Males	183	75	1.0		143	46	1.0	
Females	184	60	0.77 (0.55-1.08)	0.128	144	40	0.95 (0.61-1.48)	0.823
Tumor type								
Pheochromocytoma	263	85	1.0		211	57	1.0	
Paraganglioma	104	50	2.03 (1.43-2.89)	<0.0001	76	29	1.93 (1.20-3.12)	0.007
Tumor size (cm)	287	86	1.11 (1.06-1.15)	<0.0001	287	86	1.08 (1.04-1.13)	0.0003

Four patients with their tumor diagnosed at autopsy were excluded from overall survival analysis. Of the 371 patients, information on tumor size was available for 290.

disease. In 73% of patients with synchronous metastases, the diagnosis of malignancy was made by their referring institutions.

Overall survival by date of diagnosis

The multivariate Cox proportional hazard model showed that the overall survival of patients diagnosed with PHEO and sPGL before 1985 was not different from the overall survival of patients diagnosed with these tumors after 1985 (HR = 1.12; 95% CI = 0.62–2.04; $P = 0.70$).

Hereditary syndromic disease

In our cohort, 115 patients underwent gene testing. Seventy-three tested positive (*RET* = 43, *VHL* = 14, *SDHB* = 12, *SDHD* = 2, *SDHC* = 1, *MEN1* = 1). Three patients with metastatic PHEO carried germline *RET* mutations. *VHL* mutations were found in two patients with metastatic PHEO (DNA change c. 500 G > A and c. 457 T > C). One patient with metastatic PHEO had a MEN1 phenotype.

Genetic analysis for *SDHB*, *SDHC*, and *SDHD* mutations was introduced in our institution in 2005. Of the 21 patients with metastatic tumors analyzed for germline *SDHx* mutations, nine patients were carriers of *SDHB* mutations (43%), and one was a carrier of a *SDHC* deletion mutation (4.8%). Table 5 describes the primary tumor size and location in patients with metastatic PHEO/sPGL who were carriers of *SDHx* mutations.

Discussion

Malignant PHEOs and sPGLs are rare, aggressive tumors that are associated with decreased survival. Frequently, distant and unresectable metastases present after the primary tumor has been surgically removed. According to our study, up to 50% of patients with malignant tumors will present with metachronous metastatic disease. To date, surgery is the only treatment that can cure patients with locally recurrent or distant resectable metastasis. Unfortunately, there are no reliable histological features distinguishing between benign and malignant primary tumors. Consequently, many patients do not receive adequate follow-up care after removal of the primary tumor; this makes early identification of relapsing disease difficult, which can have devastating effects because early detection is key to a tumor's resectability. The primary tumor's characteristics, such as invasion of local blood vessels or surrounding tissue, and its size and location have been suspected to be predictors of malignancy. Given the rarity of these tumors, clinical studies have failed to confirm these aspects as predictors of malignancy and survival.

TABLE 4. Patients with pheochromocytoma with no metastasis at diagnosis

Covariates	Univariate analysis				Multivariate analysis			
	No. of patients	No. of deaths	HR (95% CI)	*P* value	No. of patients	No. of deaths	HR (95% CI)	*P* value
Age (yr)	237	67	1.04 (1.02-1.06)	<0.001	192	44	1.04 (1.02-1.06)	<0.001
Gender								
Males	109	35	1.0		87	21	1.00	
Females	128	32	0.78 (0.48-1.26)	0.314	105	23	0.85 (0.47-1.53)	0.581
Tumor size (cm)	192	44	1.09 (1.02-1.15)	0.007	192	44	1.04 (0.98-1.11)	0.178

Cox proportional hazards regression model for risk of death overall survival. Multivariate analysis could not been done in patients with sPGL with no metastases at diagnosis, given the small sample for analysis.

TABLE 5. Demographics in patients with *SDHB* and *SDHC* mutations and metastatic PHEOs and sPGLs

Age at Dx (yr)	Mutation	Primary tumor size (cm)	Dx	Location	Exon	DNA change	Status
42	*SDHB*	15	sPGL	Zuckerkandl		Complete deletion	DOD
28	*SDHB*	8.5	sPGL	Zuckerkandl		Complete deletion	NED
50	*SDHB*	10	sPGL	Zuckerkandl	2	c.112_113 ins CC	DOD
50	*SDHC*	N/A	sPGL	Zuckerkandl		Complete deletion	DOD
12	*SDHB*	N/A	sPGL	Paraaortic	7	c. 688 int G	AWD
49	*SDHB*	9	sPGL	Paraaortic	2	c.137 G>A	AWD
49	*SDHB*	4.9	sPGL	Pararenal	6	c. 642 G>C	AWD
26	*SDHB*	N/A	sPGL	Zuckerkandl	4	c.418 G>T	DOD
54	*SDHB*	3.2	Pheo	R-Adrenal	7	Arg242His	NED
31	*SDHB*	N/A	Pheo	R-Adrenal	4	c.418 G>T	NED

Dx, Diagnosis; R-Adrenal, right adrenal; N/A, not available; DOD, death of disease; NED, no evidence of disease; AWD, alive with disease.

However, we found that the size and type of the primary tumor are significantly associated with metastasis and decreased overall survival in patients with PHEO and sPGL. Patients with sPGLs had worse overall survival than patients with PHEOs. Contrary to previous findings by Goldstein *et al.* (21), who found no significant difference in the rate of malignancy between PHEOs and PGLs, we found that approximately 65–70% of patients with sPGLs originating in the infradiaphragmatic paraaortic paraganglia or the mediastinum exhibited metastases, whereas only 25% of patients with PHEOs had metastatic disease. Within the group of patients with infradiaphragmatic paraaortic sPGLs, we included tumors that originated in the organ of Zuckerkandl, the chromaffin tissue found in the paraaortic location below the inferior mesenteric artery and above the bifurcation of the aorta as originally described by the Austrian anatomopathologist Emil Zuckerkandl in 1901 (22). In our study, 66% of the sPGLs originating in the organ of Zuckerkandl were associated with metastasis. With regard to the other sPGLs, such as those originating in the bladder, a similar percentage of metastasis was found.

Despite the common origin of PHEOs/sPGLs, the mechanisms of tumorigenesis in the adrenal medulla may differ from the mechanisms of tumorigenesis in the other sympathetic ganglia. The adrenal medulla is considered a modified sympathetic autonomous nervous system ganglia. Unlike the other sympathetic ganglia, the adrenal medulla releases epinephrine directly into the blood stream because of the large amounts of phenylethanolamine N-methyltransferase. This differs from the sympathetic ganglia where norepinephrine is the main catecholamine secreted into the synaptic space. The positive regulation of phenylethanolamine N-methyltransferase by cortisol (23, 24) and the lower incidence of malignancy in PHEOs than in sPGLs led us to speculate that the adrenal cortex may impact the development of malignancy in the adrenal medulla in certain individuals. Although this has not been demonstrated in adrenal tissue, it has been suggested in thyroid tissue (interactions of follicular cells with the neuroendocrine parafollicular cells) (25).

PHEOs/sPGLs are tumors that present with variable size. It has been suggested that the risk of malignancy is associated with increasing tumor size (26, 27). There is not a clear cutoff size to distinguish benign from malignant lesions. Our findings suggest that patients with malignant tumors have decreased survival when the tumor is 5 cm or larger. However, in almost 16% of patients with metastatic tumors, the primary tumors were smaller than 5 cm. In our group, 11 (78.5%) were sPGLs, and three were PHEOs. In our series, there was a wide variability in size between metastatic and nonmetastatic tumors. For instance, a few patients with tumors as small as 2 cm had synchronous metastatic disease (lymph node metastases), and 1-cm tumors produced metastatic disease (bone) within 1 yr after surgical excision. These findings should encourage the clinician to be aggressive in early diagnosis, treatment, and follow-up and not to assume that small tumors are always benign.

In the univariate analysis, females had a trend toward a decreased risk of death, although it did not reach statistical significance. Of the three potential clinical predictors (tumor size, gender, and location), the location of the primary tumor was associated with the highest HR for death, both in univariate and multivariate analyses, followed by primary tumor size.

Since Baysal's (28) initial description of the relationship between PHEOs/sPGLs with mutations in the succinate dehydrogenase complex, the way to approach these tumors has changed. To date, 17–35% of PHEOs/sPGLs are associated with hereditary germline mutations (7, 15). Mutations in the *RET*, *NF1*, and *VHL* genes cause a phenotype mainly characterized by PHEO, whereas mutations in the *SDHx* genes are mainly associated with PGL. There is strong evidence to support the relationship between mutations of the *SDHB* gene and the presence of malignant tumors (2, 19, 29, 30). Since 2005, our institution has offered *SDHx* gene testing to all patients with

metastatic PHEO/sPGL. Nonetheless, because of its recent introduction in clinical practice, its high cost, the lack of insurance coverage, and patients' fear of discrimination or feelings of guilt for transmitting the genetic mutation to their children, most of the patients included in this study lacked genetic analysis. Now that testing is more widely available, insurance coverage of genetic testing is increasing, and with the passage of the Genetic Information Nondiscrimination Act of 2008, it is likely that more patients will have access to genetic testing without fear of insurance discrimination. We are now considering recontacting our patients and families to offer genetic testing.

Of the patients in whom genetic analysis was done, approximately 50% of metastatic tumors tested positive for germline *SDHB* mutations. In most of these patients, the disease was identified as sPGL rather than PHEO. Recently, a high prevalence of germline *SDHD* and *SDHB* mutations has been described in patients with sPGLs originating in the mediastinum and the organ of Zuckerkandl (31). Because metastatic sPGLs are not common in PGL syndrome type 1 (32, 33), we suspect that a substantial number of these patients are carriers of *SDHB* mutations. PHEO/sPGL are apparently very rare in PGL syndrome type 3 (34, 35), and their prevalence is unknown in the recently described PGL syndrome type 2 (11, 12). We found one patient with a metastatic sPGL who carried a complete *SDHC* gene deletion that was not found by regular genetic testing. Because *SDHC* gene analysis is not frequently offered to patients with metastatic PHEO or sPGL, it is possible that the prevalence of *SDHC* mutations could be higher than expected. Whether germline *SDHB* mutations are independent risk factors for metastases is the topic of further research.

Survival studies in metastatic PHEOs/PGLs are limited to small series. Sympathetic PGLs are more prone to develop metastases. When metastatic, they exhibit aggressiveness similar to that of metastatic PHEOs. These results may be surprising because *SDHB*-positive tumors (mainly sPGLs) are associated with a decreased survival (18). Therefore, the final mechanisms responsible for the appearance of metastases in both types of tumors could be similar in a substantial number of patients. In fact, many apparently sporadic PHEOs and sPGLs could display a similar and rich expression of angiogenesis, hypoxia, and extracellular matrix elements, in addition to suppression of oxidoreductase enzymes with increased intracellular hypoxia-inducible factor concentrations (36). However, in some SDHB-related PHEOs and sPGLs the HIF2 α overexpression (37) and pseudohypoxia may play an important role.

The main repercussions of this study are related to the duration of the follow-up and the surgical treatment required for patients with PHEOs/sPGLs. Approximately 35% of our patients had metastases. Although this number likely reflects a referral bias, in the context of a rare disease it strongly suggests that more than 10% of these tumors are malignant. In many of these patients, metastases were discovered years after the initial diagnosis. We recommend a long-term follow-up for individuals with sPGL, for all carriers of genetic mutations, and for all patients with tumors 5 cm or larger. The follow-ups should include biochemical studies, such as plasma metanephrines, and radiographic studies, such as computed tomography or magnetic resonance imaging. We are not able to provide follow-up guidelines on these tumors because the follow-up strategies offered to our patients were left to the discretion of each treating physician. Despite the introduction of radiographic and nuclear medicine studies in the early 1980s and the identification of biochemical markers for follow-up, the survival rates over the last 25 yr in our institution do not differ from the survival rates observed years before. Perhaps, with the introduction of early screening of susceptible individuals and the development of new therapies, the survival rates will improve. In the meantime, the experience of referral institutions on this disease must be collected and presented as guidelines to provide clinicians with specific details on how to approach patients with these rare tumors. While waiting for these guidelines to occur, an individualized multidisciplinary approach should be offered.

Our results can impact the choice of surgical approach used to resect PHEOs/sPGLs. Although the laparoscopic approach has been considered safe in patients with benign PHEOs (38), there is limited experience with metastatic PHEOs/sPGLs. The use of laparoscopy in patients with primary adrenal malignancies is controversial because laparoscopic approaches are inferior regarding nodal sampling, and there are real risks of tumor rupture in large tumors (39, 40); therefore, we suggest a cautious approach in patients with sPGL, regardless of the size of the primary tumor and for PHEOs 5 cm or larger.

Our study has some limitations, including the inherent limitations of a retrospective review. The study likely reflects a referral bias to a cancer institution. Our results should be interpreted cautiously because the rates of malignancy may not be applied population wide. Finally, we lack genetic analyses for the entire cohort.

Nevertheless, the study has multiple strengths. All pathology specimens and radiology studies have been reviewed by specialists who have confirmed the diagnosis and who have differentiated metastatic lymph nodes from multiple PGLs. Most patients have had long-term follow-up. Furthermore, to the best of our knowledge this study represents the largest series from a single institution de-

scribing the clinical factors associated with the development of metastases in patients with PHEOs/sPGLs.

In conclusion, the primary tumor size and the primary tumor location are significant clinical factors associated with metastases and decreased overall survival in patients with PHEOs/sPGLs. Many patients with these tumors need a more aggressive surgical approach at diagnosis and long-term follow-up.

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