Malignant Pheochromocytoma and Paraganglioma: 272 Patients Over 55 Years

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Context: Malignant pheochromocytoma (PHEO) and paraganglioma (PGL) are rare and knowledge of the natural history is limited.

Objective: We aimed to describe baseline characteristics and outcomes of patients with malignant PHEO and PGL (PPGL) and to identify predictors of shorter survival.

Design: Retrospective review of patients with malignant PPGL evaluated from 1960 to 2016.

Setting: Referral center.

Patients: The group comprised 272 patients.

Main Outcome Measures: Baseline description, survival outcomes, and predictors of shorter survival were evaluated in patients with rapidly progressive (n = 29) and indolent disease (n = 188).

Results: Malignant PPGL was diagnosed at a median age of 39 years (range, 7 to 83 years), with synchronous metastases in 96 (35%) patients. In 176 (65%) patients, metastases developed at a median of 5.5 years (range, 0.3 to 53.4 years) from the initial diagnosis. Median follow-up was 8.2 years (range, 0.01 to 54.1 years). Median overall and disease-specific survivals were 24.6 and 33.7 years, respectively. Shorter survival correlated with male sex ($P = 0.014$), older age at the time of primary tumor ($P = 0.0011$), synchronous metastases ($P < 0.0001$), larger primary tumor size ($P = 0.0039$), elevated dopamine ($P = 0.0195$), and not undergoing primary tumor resection ($P < 0.0001$). There was no difference in the type of primary tumor or presence of *SDHB* mutation.

Conclusions: The clinical course of patients with malignant PPGL is remarkably variable. Rapid disease progression is associated with male sex, older age at diagnosis, synchronous metastases, larger tumor size, elevated dopamine, and not undergoing resection of primary tumor. An individualized approach to patients with metastatic PPGL is warranted. **(*J Clin Endocrinol Metab* 102: 3296–3305, 2017)**

Pheochromocytoma (PHEO) and paraganglioma (PGL) are neuroendocrine tumors arising from chromaffin cells of the adrenal medulla and extra-adrenal autonomic paraganglia, respectively. The combined estimated annual incidence of PHEO and PGL (PPGL) is ~0.8 per 100,000 person-years (1), and there are ~500 to 1600 new cases in the United States per year (2). Patients with catecholamine-secreting PPGL frequently present with symptoms of catecholamine excess, whereas nonfunctioning PPGL may cause local compressive symptoms due to bulky disease (3, 4). More than 30% of patients with PPGL have a hereditary predisposition, and up to 50% of patients with metastatic disease have certain hereditary germline mutations (3, 4). Syndromic

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Abbreviations: CI, confidence interval; MEN, multiple endocrine neoplasia; NF1, neurofibromatosis type 1; OR, odds ratio; PGL, paraganglioma; PHEO, pheochromocytoma; PPGL, pheochromocytoma and paraganglioma; SDH, succinate dehydrogenase; TMEM127, transmembrane protein 127; VHL, von Hippel–Lindau.

PPGL is seen as a part of multiple endocrine neoplasia (MEN) type 2, von Hippel–Lindau (*VHL*) disease, and neurofibromatosis type 1 (NF1). Hereditary PPGL is mainly seen with mutations in succinate dehydrogenase (SDH) subunits (5, 6). Less common germline mutations associated with PPGL include mutations in transmembrane protein 127 (*TMEM127*), myc-associated factor X genes, somatic gain-of-function mutations in the gene encoding hypoxia-inducible factor 2α, and pathogenic germline mutations in the *FH* gene encoding fumarate hydratase (7–10).

According to the World Health Organization, the diagnosis of malignant PPGL requires evidence of metastases at nonchromaffin sites distant from the primary tumor, such as lymph nodes, bones, liver, lung, brain, and others (11). Malignant disease has been reported in 2% to 13% of patients with PHEO and 2.4% to 50% with PGL (12–14). At least 11% of all patients with PPGL and up 31% of patients with PPGL in the setting of predisposing genetic mutation present with synchronous metastatic disease at the time of primary tumor diagnosis (15, 16). Predicting malignant disease in patients presenting with primary tumor without metastases is difficult, and there are no reliable clinical, molecular, histopathological, or biochemical markers of malignant potential. Mitotic activity, cellular atypia, or vascular invasion do not reliably predict malignant predisposition of these tumors. Moreover, the extent of local invasion to adjacent tissues does not necessarily indicate higher risk toward development of metastases (4).

Owing to the rarity of PPGL in general, and metastatic disease especially, current evidence on the natural history of malignant PPGL is scarce. Limited data exist with regard to clinical outcomes of patients with malignant disease; most reports are based on small, highly selected cohorts of patients. The objectives of the present study were to assess overall and disease-specific survival rates of patients with malignant PPGL. We also aimed to describe baseline characteristics and outcomes of patients with malignant PPGL and to identify prognostic factors influencing the course of the disease.

Subjects and Methods

Subjects

To examine the predictive features associated with shorter overall and disease-specific survival, we retrospectively reviewed a consecutive cohort of patients with malignant PPGL evaluated at the Mayo Clinic (Rochester) between 1 January 1960 and 30 September 2016. The study was approved by the Institutional Review Board of the Mayo Clinic. The Mayo Clinic PPGL database was reviewed to identify patients with malignant PPGL. Of 3280 patients, 272 (8.3%) had malignant disease. Diagnosis was confirmed by reviewing clinical, histopathological, and biochemical data. PGL was categorized according to the location of the primary tumor. Patients with both PHEO and PGL were included in the PGL group. Malignant disease was defined in accordance with the 2004 World Health Organization criteria (17). Synchronous metastatic disease was defined as the presence of distant metastases at the time or within 3 months of the primary tumor diagnosis. Patients who developed metastatic disease $\geq$3 months after the diagnosis of the primary tumor were defined to have metachronous metastases. Patients were characterized to have a genetic mutation predisposing to PPGL if they had a documented genetic testing for major PPGL susceptibility genes, familial history of genetic mutation, or presence of at least two National Institutes of Health criteria for diagnosing NF1 syndrome.

All PPGL tumors were defined as functional when urine or plasma-fractionated catecholamines or fractionated or total metanephrines were elevated above the upper limit of respective reference ranges. The reference intervals for plasma concentrations were established at the Mayo Clinic (18). The tumors were considered nonfunctional when the levels of plasma or urine metanephrines/catecholamines remained within the reference ranges. Tumors hypersecreting primarily epinephrine/metanephrine or norepinephrine/normetanephrine were termed adrenergic and noradrenergic, respectively. We separately evaluated for dopamine hypersecretion in all tumors and termed them dopaminergic. To investigate whether the time period of diagnosis played a role in baseline characteristics and outcomes of patients with malignant PPGL, we analyzed the variables based on year of diagnosis using the following arbitrary time intervals: 1960 to 1990 and 1991 to 2016. Additionally, for more detailed evaluation of prognostic factors for disease progression, we identified the patients with at least 5 years of follow-up from the primary tumor diagnosis, unless preceded by death due to malignant PPGL, and divided the cohort into two groups: patients with rapidly progressive disease who died of malignant PPGL within 5 years of the primary tumor diagnosis, and patients with indolent disease with at least 5-year disease survival. Patients with $<$5 years of follow-up, or those who died of other causes within 5 years of primary tumor diagnosis, were excluded from this analysis.

Data analysis

Descriptive statistics were used to provide a summary of the data. Categorical data were given as absolute and relative frequencies (percentages). Continuous data were presented as median, minimum to maximum range. To compare medians between two independent groups, we used the nonparametric Wilcoxon rank sum test. In patients with at least 5 years of follow-up after primary diagnosis, logistic regression models were used to estimate association of risk factors of dying within 5 years. Because there were 29 deaths in the rapidly progressive group, a multivariate logistic regression model was fit using three predictors, based on 10 events per predictor rule. The variables chosen to be in the multivariate model were based on those reported in prior studies. All tests were two-sided, and P values < 0.05 were considered statistically significant. All statistical analyses were conducted using JMP version 10 (SAS Institute, Cary, NC).

Results

Patient demographics

Between 1960 and 2016, 272 patients (138, 51% women) were diagnosed with malignant PHEO (n = 97,

36%), PGL (n = 159, 58%), or both (n = 16, 6%) (Table 1). Patients presented with the primary tumor at the median age of 39 years (range, 7 to 83 years).

Although most cases of PPGL were apparently sporadic (191 patients, 70%), in 81 (30%) patients PPGL occurred in the context of a hereditary syndrome: 42 (15.4%) patients with *SDHB* mutation; 7 (2.6%) with *SDHD* mutation; 4 (1.5%) with *NF1*; 3 (1.1%) with VHL disease; 3 (1.1%) with MEN type 1 (*MEN1)*; 3 (1.1%) with MEN type 2A; 2 (0.7%) with *SDHC*; 1 (0.4%) with Carney triad; and 1 (0.4%) with a *TMEM127* mutation. Fifteen patients (5.5%) were diagnosed with familial PPGL based on family history (Table 1).

Table 1. Patient Characteristics

Characteristic	Data
N	272
Male	134 (49%)
Female	138 (51%)
PHEO	97 (36%)
PGL	159 (58%)
Both[a]	16 (6%)
Tumor location	
Abdomen/pelvis	110 (40%)
Adrenal[b]	106 (40%)
Skull base and neck	31 (11%)
Thorax	19 (7%)
Other	6 (2%)
Genetic status	
Familial (including patients with NF1 and confirmed germline mutation)	66 (24%)
Probably familial (nonconfirmed germline mutation but strong family history)	15 (6%)
Tested negative[c]	36 (13%)
Not done/insufficient information	155 (57%)
Age at primary tumor diagnosis, y	39 (7–83)
Synchronous metastasis	96 (35%)
Regional metastasis (proximal lymph nodes and soft tissues)	28/96 (29%)
Distant metastasis	68/96 (71%)
Age at diagnosis of metastases, y	44 (7–84)
Time to metachronous metastases, y	5.5 (0.3–53.4)
Duration of follow up from primary diagnosis, y	8 (0–54)
Duration of follow-up from metastases, y	4 (0–40)
Status	
Alive with disease	154 (57%)
No evidence of disease	18 (6%)
Died of disease	73 (27%)
Died of other causes	27 (10%)
Age at death, y	54 (7–91)

Categorical data are presented as absolute and relative frequencies (percentages). Continuous data are presented as median (minimum–maximum range).

[a]For statistical analysis, patients with both PHEO and PGL were included in the PGL group (PHEO 97, 36% and PGL 175, 64%).

[b]Fifty (47%) patients had right PHEO, 50 (47%) patients had left PHEO, and 7 (6%) patients had bilateral PHEO. One patient with bilateral PHEO also had PGL and was included in the PGL group.

[c]Of 36 patients, 30 (83%) patients tested negative for an *SDHB* mutation.

PPGL was preceded by adrenergic symptoms (*e.g.*, spells, hypertension, headache, palpitations) in 137 (50%) patients, by tumor-related mass effect (lump, pain, compression of surrounding structures) in 70 (26%) patients, or discovered incidentally on imaging in 65 (24%) patients. Median size of the primary tumor at the time of the initial diagnosis of PPGL was 7.0 cm (range, 0.9 to 26.0 cm). Of 248 patients with sufficient biochemical testing data, catecholamine hypersecretion was observed in 197 (79%) patients (Table 2).

Ninety-six (35%) patients presented with synchronous metastases, whereas 176 (65%) patients developed metachronous metastases at a median of 5.5 years (range, 0.3 to 53.4 years) after the primary tumor diagnosis (Table 1). The most common locations of metastases were bone (n = 161, 59.1%), lymph nodes (n = 127, 46.7%), liver (n = 99, 36.4%), lungs/thorax (n = 103, 37.9%), and abdomen/pelvis (n = 86, 31.6%).

Surgery was the most common treatment of primary tumors (n = 243, 89.3%). Twenty-eight (10.3%) patients were determined to have unresectable tumors; one (0.4%) patient was a poor surgical candidate due to comorbidities. Out of 164 patients, 159 (97%) patients underwent additional surgical resection (for reoperation of primary tumors or metastasectomy). Palliative radiotherapy was performed in 128 (47%) patients. Ninety-five (35%) patients received chemotherapy and targeted molecular therapy (cyclophosphamide, vincristine,

Table 2. Tumor Characteristics

Characteristic	Data
Primary tumor size, cm	7.0 (0.9–26.0)
Multifocal PHEO/PGL	66 (24%)
Functional[a]	197/248 (79.4%)
Noradrenergic	113/177 (63.8%)
Adrenergic	61/177 (34.5%)
Dopaminergic[b]	72/172 (42%)
Nonfunctional	51/248 (21%)
Mode of discovery of primary tumor	
Asymptomatic/incidental	65 (24%)
Adrenergic symptoms	137 (50%)
Mass effect symptoms	70 (26%)
Recurrence at the primary tumor site	90 (33%)
Time to recurrence, y	4.1 (0.2–34.9)
Surgical resection of the primary tumor	243 (89.3%)
Unresectable	28 (10.3%)
Poor surgical candidacy due to comorbidities	1 (<1%)

Categorical data are presented as absolute and relative frequencies (percentages). Continuous data are presented as median (minimum–maximum range).

[a]Of 272 patients, 248 patients underwent biochemical testing and 24 (9%) patients did not complete testing. Of 248 patients, biochemical profile was uncharacterizable in 20 (8%) patients.

[b]Sufficient laboratory data on dopamine hypersecretion was available in 172 patients.

dacarbazine, everolimus, sunitinib, sorafenib, pazopanib, lenvatinib, and others), 25 (9%) had radiofrequency ablation, 24 (8.8%) had ^{131}I-metaiodobenzylguanidine treatment, 16 (5.8%) had embolization procedures, 13 (4.7%) had stereotactic radiotherapy, 11 (4%) had cryoablation, and 2 (0.7%) had percutaneous ethanol injection.

Patients were followed for a median of 8.2 years (range, 0.01 to 54.1 years) from the initial diagnosis and for a median of 4.0 years (range, 0.01 to 40 years) from the time of metastatic spread. Among patients with <1 year of follow-up (n = 15, 6%), 53% died of disease, 7% died of other causes, and 40% were alive at last follow-up. Among patients with 1 to 5 years of follow-up (n = 69, 25%), 31% died of disease, 7% died of other causes, and 62% were alive at last follow-up. Of those with 5 to 10 years of follow-up (n = 66, 24%), 26% died of disease, 10% died of other causes, and 64% were alive with disease. One hundred twenty-two patients (45%) had >10 years of follow-up: 22% died of disease, 12% died of other causes, and 66% were alive with disease at last follow-up (Fig. 1).

Among patients alive at last follow-up, median duration of follow-up was 8.8 years (range, 0.01 to 54.1 years) and 4.7 years (range, 0 to 38.0 years) from the initial tumor diagnosis and metastases, respectively. At the conclusion of the study, 154 (57%) patients were alive with disease and 18 (6%) patients had disease remission.

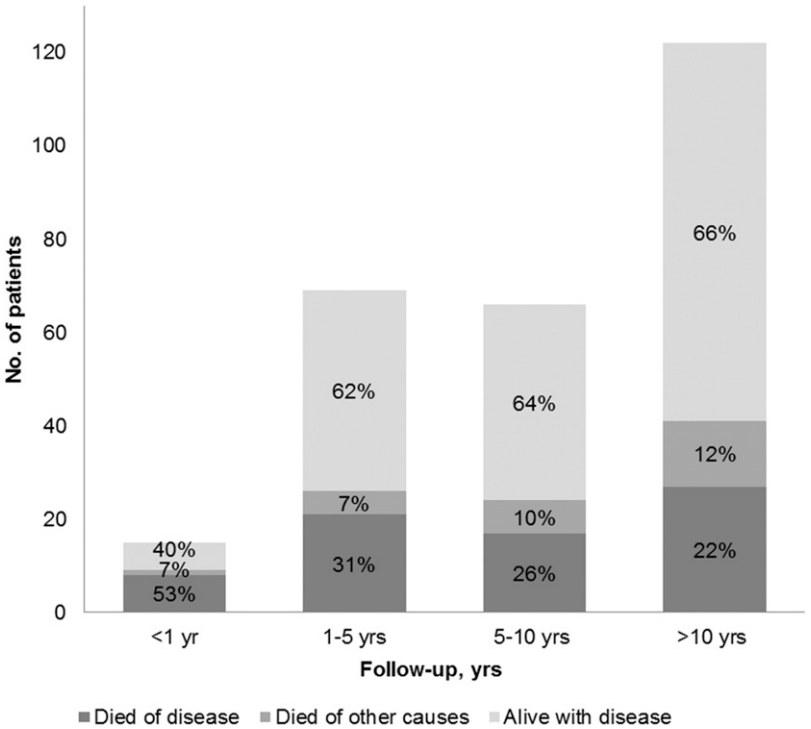

Figure 1. Outcomes of patients with malignant PPGL based on the duration of follow-up. Duration of follow-up was <1 year in 15 (6%) patients, 1 to 5 years in 69 (25%) patients, 5 to10 years in 66 (24%) patients, and >10 years in 122 (45%) patients.

One hundred (37%) patients died during follow-up; 73 (27%) patients died of malignant PPGL and 27 (10%) patients died of causes unrelated to PPGL. In 73 (27%) patients who died of malignant PPGL, the median survival was 6 years (range, 0.01 to 41 years) and 3 years (range, 0.01 to 17 years) from primary diagnosis and development of metastasis, respectively (Table 1).

Year of diagnosis

Of 272 patients, 97 (54.6% women) were diagnosed between 1960 and 1990, and 175 patients (48.6% women) were diagnosed between 1991 and 2016. Among those diagnosed before 1990 vs after 1990, more patients presented with adrenergic symptoms (n = 61, 62.9% vs n = 76, 43.4%; $P = 0.002$), a similar proportion presented with mass effect symptoms (n = 24, 24.7% vs n = 46, 26.3%; $P = 0.78$), and fewer were diagnosed incidentally (n = 12, 12.4% vs n = 53, 30.3%; $P = 0.0006$) (Supplemental Table1).

There was no between-group differences in tumor size ($P = 0.57$), rate of surgical resection of primary tumor ($P = 0.89$), functional PPGL ($P = 0.22$), or proportion of patients with rapid disease progression ($P = 0.34$) (Supplemental Table 1).

Primary tumor type

Patients with malignant PHEO (n = 97, 36%) and PGL (n = 175, 64%) had similar sex distribution ($P = 0.58$). Compared with PGL, PHEOs were larger [median size 9.0 cm (range, 3.0 to 26.0 cm) vs 5.8 cm (range, 0.9 to 19.1 cm); $P < 0.0001$], more frequently functional (91% vs 72%; $P = 0.0001$), and less commonly associated with *SDHB* mutation (1.0% vs 23.4%; $P < 0.0001$). Additionally, both groups had a similar rate of surgical resection of primary tumors (94% vs 87%; $P = 0.064$) and time interval from primary tumor to discovery of metastases [2.7 years (range, 0 to 34.2 years) vs 2.1 years (range, 0 to 53.4 years); $P = 0.21$] (Supplemental Table 2).

Compared with PHEO, PGL was more commonly diagnosed at a younger age [median, 36 years (range, 7 to 82 years) vs 46 years (range, 11 to 83 years); $P < 0.0001$]. Additionally, patients with PGL were more likely to have a noradrenergic biochemical phenotype (76.0% vs 50.0%; $P = 0.0004$), more likely to have synchronous metastatic disease (41% vs 26%;

$P = 0.013$), and more likely to have multifocal disease (33% vs 8%; $P < 0.0001$) (Supplemental Table 2).

Patients with malignant PGL had more bone (67% vs 45%; $P = 0.0006$) and lymph node (53% vs 35%; $P = 0.004$) metastases compared with PHEO, whereas liver metastases were more common in patients with PHEO (49% vs 30%; $P = 0.002$). There were no differences in the rates of lung/thoracic, abdominal/pelvic, or brain metastases between groups ($P > 0.05$). Importantly, there were no differences between rapidly progressive and indolent metastatic disease among PHEO and PGL ($P = 0.14$) and disease-specific mortality ($P = 0.07$) (Supplemental Table 2).

Risk of rapid disease progression

Among patients with sufficient follow-up, 29 patients had rapid disease progression (<5 year survival from the time of primary tumor diagnosis) and 188 patients had indolent disease (alive for at least 5 years from the time of diagnosis) (Table 3). Univariate analysis demonstrated that rapid disease progression was associated with male sex (n = 20, 69% vs n = 84, 45%; $P = 0.014$), older age at primary tumor diagnosis [50 years (range, 7 to 70 years) vs 36 years (range, 9 to 83 years); $P = 0.0011$], synchronous metastases (n = 22, 76% vs n = 40, 21%; $P < 0.0001$), larger primary tumor size [10.0 cm (range, 1.0 to 19.1 cm) vs 6.4 cm (range, 0.9 to 22.0 cm); $P = 0.0039$], elevated dopamine levels (n = 10, 71% vs n = 49, 39%; $P = 0.0195$), and not undergoing surgical resection of primary tumor (19, 66% vs 181, 96%; $P < 0.0001$) (Table 4). None of the patients with skull base and neck PGL had rapid disease progression. Additionally, patients with rapidly progressive disease more frequently developed lung/thoracic metastases (n = 17, 59% vs n = 67, 36%; $P = 0.0197$). There was a similar distribution among other metastatic sites between the groups.

There were no between-group differences in the year of primary tumor diagnosis (1995 vs 1991), type of primary tumor (48% vs 34% PHEOs, 52% vs 66% PGL), age at diagnosis of metastases (50 vs 43 years), or presence of *SDHB* mutation (10% vs 17%) (Table 3).

Fewer patients in the rapidly progressive group underwent reoperation of primary tumors or metastasectomy (n = 10, 35% vs n = 138, 73%; $P < 0.0001$). Patients with rapidly progressive disease more commonly received chemotherapy (n = 17, 59% vs n = 59, 31%; $P = 0.0052$).

Multivariate analysis showed that independent factors associated with rapid disease progression and mortality in patients with malignant PPGL included: older age at primary diagnosis [odds ratio (OR) = 1.04; 95% confidence interval (CI), 1.01 to 1.08; $P = 0.0047$, for 1 year age difference], larger tumor size (OR = 1.12; 95% CI, 1.009 to 1.25; $P = 0.034$, for each 1 cm increase in tumor size), and synchronous metastases (OR = 10.24, 95% CI 3.76 to 31.18; $P < 0.0001$) (Table 4).

Median overall survival was 24.6 years for patients with malignant PPGL (Fig. 2). The 5-year overall survival rate was 85.4% (79.2% for PHEO, 88.9% for PGL), 10-year overall survival rate was 72.5% (64.2% for PHEO, 77.3% for PGL), and 15-year overall survival was 65.4%. Median disease-specific survival was 33.7 years. Disease-specific survival rate was 88.1% at 5 years, 77.9% at 10 years, and 71.8% at 15 years. Overall and disease-specific survival rates were similar for patients with metastatic PHEO and PGL ($P = 0.22$ and $P = 0.87$).

Discussion

We found that the clinical behavior of malignant PPGL is remarkably variable. For example, whereas in some patients discovery of metastases precedes discovery of the primary tumor, others develop metastases >50 years after the initial diagnosis.

We observed a median overall survival of 24.6 years and a median disease-specific survival of 33.7 years. Previous reports on the clinical course of metastatic PPGL have been widely inconsistent, with the 5-year survival rates ranging from 12% to 84% (4, 19–23). Without treatment, the 5-year survival rate has been reported to be generally <50% (24). In contrast, our study showed that overall and disease-specific 5-year survival rates were 85.4% and 88.2%, and 10-year overall and disease-specific survival rates were 72.5% and 77.9%, respectively. These results indicate that a substantial number of patients have an excellent prognosis despite having malignant PPGL. Similar to previous reports, we found that the course of the disease can be highly variable with some patients living >50 years after diagnosis (25, 26).

We found that male sex, older age at primary tumor diagnosis, dopamine hypersecretion, synchronous metastases, larger primary tumor size, and not undergoing surgical resection of the primary tumor were associated with an aggressive disease course and higher mortality risk. On the multivariate analysis, older age at primary tumor diagnosis, larger primary tumor size, and presence of synchronous metastases remained significant predictors of rapid disease progression and death. Comparable to our findings, others have previously reported that male sex (20), older age at the primary tumor diagnosis (age ≥ 76 years) (20, 27), and failure to undergo surgical resection of the primary tumor (20–22) were associated with shorter survival (20).

In our study, larger primary tumor size was associated with rapid disease progression and higher mortality risk.

Table 3. Characteristics of Patients With Rapidly Progressive and Indolent Disease Course

	Rapidly Progressive (n = 29)	Indolent (n = 188)	*P* Value
Male	20 (69%)	84 (45%)	0.014
Female	9 (31%)	104 (55%)	
Primary tumor type			0.1433
PHEO	14 (48%)	64 (34%)	
PGL	15 (52%)	124 (66%)	
Location of primary tumor			
Adrenal	15 (52%)	71 (38%)	0.1568
Abdomen/pelvis PGL	12 (41%)	77 (41%)	0.9657
Thorax	1 (3%)	13 (7%)	0.4455
Skull base and neck	0	25 (13%)	0.0057
Other	1 (3%)	2 (1%)	—
Mode of discovery			
Adrenergic symptoms	11 (38%)	109 (58%)	0.0436
Mass effect	10 (34%)	43 (23%)	0.190
Incidental/asymptomatic	8 (28%)	36 (19%)	0.309
Genetic status			
Sporadic	24 (83%)	123 (65%)	0.0512
SDHB	3 (10%)	32 (17%)	0.340
SDHC	0	2 (1%)	—
SDHD	0	7 (4%)	—
Familial	0	14 (7%)	—
MEN1	1 (3%)	2 (1%)	—
NF1	0	3 (1.6%)	—
MEN2A	1 (3%)	2 (1%)	—
VHL	0	1 (0.5%)	—
TMEM127	0	1 (0.5%)	—
Carney	0	1 (0.5%)	—
Year of primary diagnosis	1991 (1965–2012)	1995 (1951–2011)	0.8174
Age at primary diagnosis, y	50 (7–70)	36 (9–83)	0.0011
Primary tumor size, cm	10.0 (1.0–19.1)	6.4 (0.9–22.0)	0.0039
Functional (n = 202 tested)	21/27 (78%)	141/175 (81%)	0.7377
Noradrenergic	8/27 (29.6%)	82/175 (46.9%)	0.093–0.669
Adrenergic	8/27 (29.6%)	45/175 (25.7%)	0.0195
Dopaminergic	10/14 (71.4%)	49/126 (38.9%)	
Biochemical profile at last follow-up	20/21 (95%) functional	117/141 (83%) functional	0.1024
Nonfunctional	1/21 (5%) biochemical remission	24/141 (17%) biochemical remission	0.1570
Uncategorizable	6/27 (22.2%)	34/175 (19.4%)	0.7345
	5 (18.5%)	13 (7.4%)	0.0598
Multifocal	5 (17%)	51 (27%)	0.2400
Surgical resection of primary tumor	19 (66%)	181 (96%)	<0.0001
Recurrent tumors	2 (7%)	77 (41%)	<0.0001
Time to recurrence, y	1.4 (0.7–2.1)	6.9 (0.2–34.9)	0.0657
Synchronous	22 (76%)	40 (21%)	<0.0001
Regional vs distant	1 (5%) vs 21 (95%)	16 (40%) vs 24 (60%)	0.0010
Age at metastatic disease, y	50 (7–70)	43 (13–84)	0.3004
Time from diagnosis to metachronous metastasis, y	0.5 (0.4–2.4)	6.2 (0.4–53.4)	<0.0001
Death related to disease	29 (100%)	44 (68%)	<0.0001
Age at death, y	54 (7–71)	54 (26–91)	0.0685
Time to last follow-up/death, y	1.6 (0.1–4.5)	12.3 (5.0–54.1)	<0.0001
Status			<0.0001
Alive with disease	0	107 (57%)	
No evidence of disease	0	16 (9%)	
Died of disease	29 (100%)	44 (23%)	
Died of other causes	0	21 (11%)	

Categorical data are presented as absolute and relative frequencies (percentages). Continuous data presented as median (minimum–maximum range).

Similarly, larger tumor size (generally >4.5 to 5 cm) has been reported as a strong predictor of persistent or recurrent disease and mortality in several other studies (4, 20, 24, 28, 29). In one study, primary tumor size ≥ 6 cm was found to be an important independent risk factor for metastatic disease (30), and tumor size was

Table 4. Univariate and Multivariate Analyses for Risk of Rapidly Progressive Disease

	Univariate Analysis		Multivariate Analysis	
Variables	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Sex				
Males	2.75 (1.22–6.65)	0.014		
Females	0.36 (0.15–0.81)			
Age at diagnosis (per 1 y)	1.04 (1.02–1.07)	0.0018	1.04 (1.01–1.08)	0.0047
Tumor size (per 1 cm)	1.14 (1.04–1.27)	0.0039	1.12 (1.009–1.25)	0.034
Dopamine secretion	3.93 (1.24–14.96)	0.0195		
Synchronous	11.63 (4.85–31.22)	<0.0001	10.24 (3.76–31.18)	<0.0001
Not undergoing surgery	13.61 (4.71–41.62)	<0.0001		

significantly associated with worse overall survival after adjusting for age, sex, and tumor location (23). Another study reported that in *SDHB*-related PPGL the size of the primary tumor predicts development of metastatic disease and also affects patient survival (31).

We observed an association between dopamine hypersecretion and more aggressive malignant disease. High plasma and urinary levels of dihydroxyphenylalanine and dopamine, the immediate precursors of norepinephrine, are biochemical markers that may characterize malignant PPGL (24, 32, 33). These markers suggest a dedifferentiated state suggestive of malignant potential; however, they do not accurately discriminate benign from malignant disease.

Similar to our results, the timing of metastasis was an important determinant of prognosis in other studies (4, 20, 23). Presence of synchronous metastases has been associated with shorter survival, whereas onset of metastasis >6 months after the initial diagnosis or resection of the primary tumor had longer overall survival durations than in patients with synchronous metastasis.

In our study, patients with malignant skull base and neck PGL had indolent courses of disease with longer survival (overall 5-year survival rate was 85.4% and 5-year disease-specific survival rate was 88.2%). Among patients with sufficient follow-up, none with malignant skull base and neck PGL died of disease within 5 years of primary diagnosis. Similarly, others showed that 5-year overall survival was 88.1% for surgery alone and 66.5% for adjuvant radiation ($P = 0.23$) for 86 patients with malignant skull base and neck PGL (34). In contrast, another study that evaluated prognosis of 59 patients with skull base and neck PGL metastatic to regional lymph nodes and distant sites reported a much shorter 5-year relative survival rate of 59.5% (21).

Interestingly, we did not find that primary tumor type, multifocal PPGL, location of primary tumor (except skull base and neck), functional biochemical status, or presence of *SDHB* mutation played a significant role in the progression of malignant disease. Germline mutations of the *SDHB* gene are considered one of the most important risk factors for developing metastatic PPGL, with rates up to 50% to 90% in some studies (3, 23, 35–37). Previous studies have also reported that in cases of malignant PPGL, *SDHB* mutation was identified in 5% to 10% of patients (38). In contrast to our findings, these mutations have been associated with more aggressive tumor behavior than other PPGL types (3, 4, 23, 35–37). Patients with malignant *SDHB*-positive PPGL were reported to have a shorter overall survival (5-year survival probability 0.36, relative risk 2.6; $P = 0.019$) compared with patients with malignant PPGL not associated with *SDHB* mutations (35). Another retrospective review found that adult patients with *SDHB* mutations had statistically worse survival than did those with apparently sporadic disease (39).

We found no difference in survival rates among patients with malignant PHEO and PGL. In contrast to our findings, others have reported that patients with PHEO had longer overall survival (73.3% vs 54.0%; $P = 0.001$) compared with PGL, although disease-specific survival rates were similar (80.5% vs 73.5%, respectively; $P = 0.118$) (20).

Our study included a large number of patients with malignant PPGL. Given the retrospective design of this study, follow-up of patients varied based on clinical and patient decisions. Nevertheless, the design of the study allowed for a long follow-up of patients, otherwise not feasible in a prospective study. Most patients with a rare malignant disease are followed at tertiary centers, and thus it is likely that our cohort is representative. It is possible that patients with more aggressive disease were more likely to be referred and followed at our institution. Additionally, differences between rapidly progressive and indolent cohort may in part be due to delayed presentation of patients with the rapidly progressive disease. The reasons for better prognosis in our cohort in comparison with others could be explained by referral bias,

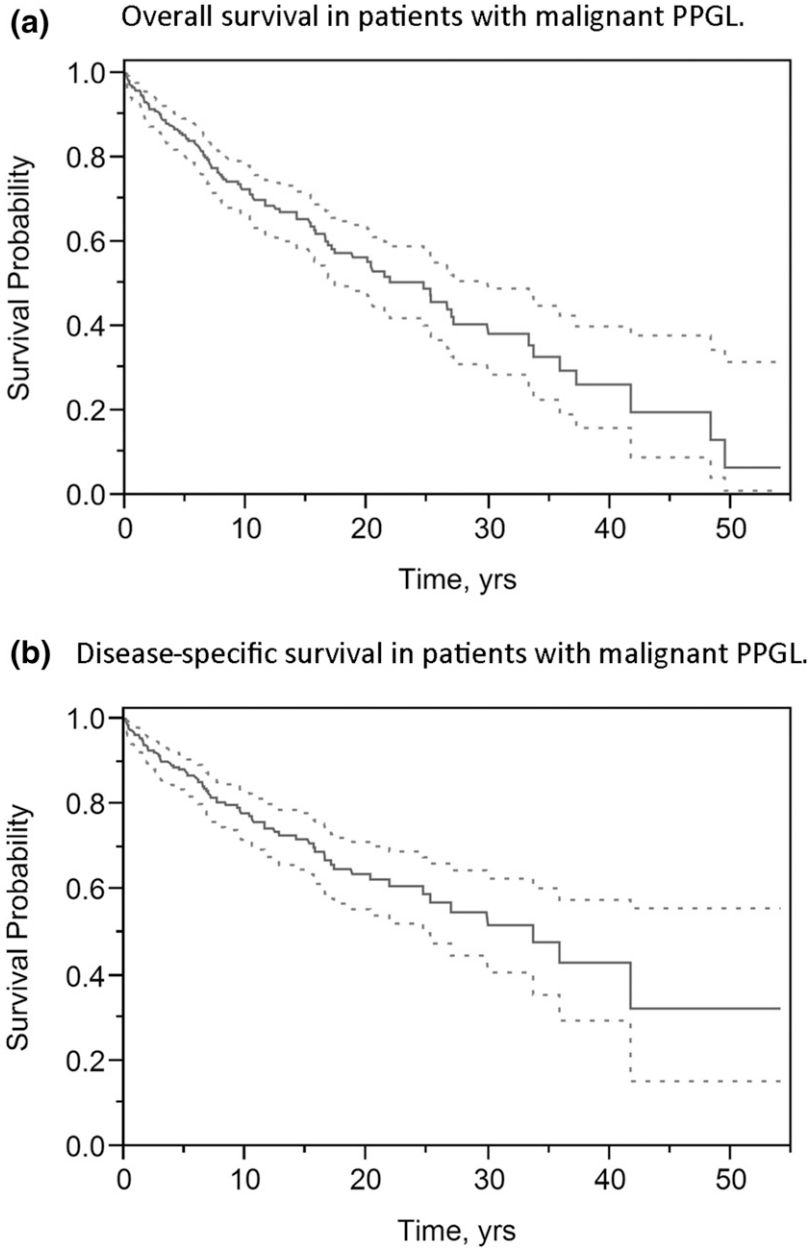

Figure 2. Overall and disease-specific survival in patients with malignant PPGL. (a) Overall survival in patients with malignant PPGL. (b) Disease-specific survival in patients with malignant PPGL.

longer duration of follow-up than most other studies, and inclusion of a nonselective cohort.

Conclusion

In conclusion, patients with malignant PPGL have a markedly variable course of the disease and longer overall and disease-specific survival than previously reported. Although death can occur within a year of diagnosis, metastatic disease can be stable for >40 years. Detection of metastases can occur prior to the detection of primary tumors, but metastatic spread can also be discovered >50 years after the primary diagnosis. Therefore, lifelong follow-up of patients with PPGL is indicated. Larger tumor size, older age at diagnosis, and failure to undergo surgery could be indicators of delayed diagnosis and may be avoidable in some patients. Additionally, these factors, along with synchronous metastases and dopamine hypersecretion, could represent intrinsically more aggressive disease. Thus, a multidisciplinary and individualized approach to treatment of patients with metastatic PPGL is warranted.

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