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Original Research

Determinants of disease-specific survival in patients with and without metastatic pheochromocytoma and paraganglioma

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KEYWORDS
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Abstract ***Background:*** Pheochromocytomas and paragangliomas (PPGLs) have a heterogeneous prognosis, the basis of which remains unclear. We, therefore, assessed disease-specific survival (DSS) and potential predictors of progressive disease in patients with PPGLs and head/neck paragangliomas (HNPGLs) according to the presence or absence of metastases.

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Predictors;
Survival;
Methoxytyramine

Methods: This retrospective study included 582 patients with PPGLs and 57 with HNPGLs. DSS was assessed according to age, location and size of tumours, recurrent/metastatic disease, genetics, plasma metanephrines and methoxytyramine.

Results: Among all patients with PPGLs, multivariable analysis indicated that apart from older age (HR = 5.4, CI = 2.93–10.29, P < 0.0001) and presence of metastases (HR = 4.8, CI = 2.41–9.94, P < 0.0001), shorter DSS was also associated with extra-adrenal tumour location (HR = 2.6, CI = 1.32–5.23, P = 0.0007) and higher plasma methoxytyramine (HR = 1.8, CI = 1.11–2.85, P = 0.0170) and normetanephrine (HR = 1.8, CI = 1.12–2.91, P = 0.0160). Among patients with HNPGLs, those with metastases presented with longer DSS compared to patients with metastatic PPGLs (33.4 versus 20.2 years, P < 0.0001) and only plasma methoxytyramine (HR = 13, CI = 1.35–148, P = 0.0380) was an independent predictor of DSS. For patients with metastatic PPGLs, multivariable analysis revealed that apart from older age (HR = 6.2, CI = 3.20–12.20, P < 0.0001), shorter DSS was associated with the presence of synchronous metastases (HR = 4.9, CI = 2.78–8.80, P < 0.0001), higher plasma methoxytyramine (HR = 2.4, CI = 1.44–4.14, P = 0.0010) and extensive metastatic burden (HR = 2.1, CI = 1.07–3.79, P = 0.0290).

Conclusions: DSS among patients with PPGLs/HNPGLs relates to several presentations of the disease that may provide prognostic markers. In particular, the independent associations of higher methoxytyramine with shorter DSS in patients with HNPGLs and metastatic PPGLs suggest the utility of this biomarker to guide individualized management and follow-up strategies in affected patients.

1. Introduction

Pheochromocytomas and paragangliomas (PPGLs) are neuroendocrine tumours derived from chromaffin cells or their neural crest-derived precursors in respective adrenals or extra-adrenal paraganglia [1]. Although sympathetic paragangliomas usually produce norepinephrine and/or dopamine, parasympathetic tumours located in the head and neck (HNPGLs) are mostly non-functional or produce dopamine [2]. More than 30% of all patients with PPGLs and HNPGLs have a hereditary predisposition [3,4], and approximately 20% can develop metastases [5]. Biochemical diagnosis of PPGLs is most accurately achieved by measurements of plasma free normetanephrine (NMN) and metanephrine (MN), the O-methylated metabolites of catecholamines [6]. Measurements of plasma free methoxytyramine (MTY) are particularly useful for the detection of dopamine producing tumours [7].

Survival is the most reliable primary end-point to assess the prognosis of cancer in clinical studies [8]. However, overall survival (OS) bears a major limitation, the inclusion of non-tumour-related death. Disease-specific survival (DSS), on the other hand, is directly associated with progression free survival and is increasingly used as a superior prognostic parameter that represents better the extent and reliability of prognostic evidence for patients with cancer.

Prognostic studies on PPGLs have been mainly limited to OS, with five-year survival rates ranging between 65 and 85% [9–12]. Predictors of the poor OS include larger primary tumour size, extra-adrenal tumour location, and older age [11,12]. As expected, the presence of metastases is strongly related to higher mortality, with five-year OS rates ranging between 12 and 84% [13–15]. Among patients with metastases, the presence of *SDHB* mutations and synchronous metastases for those with PPGLs [13–15] older age, and extensive metastatic disease for those with HNPGLs [16–18], have been associated with poor OS.

Only in recent studies has DSS been introduced to assess prognosis in patients with metastatic PPGLs [19–21]. These studies indicate that older age, high levels of metanephrines, and larger tumour size stand out as independent predictors of DSS. However, the prognostic value of the genetic background or the time interval between initial tumour presentation and diagnosis of metastases for DSS remains controversial [19–21]. Despite the clear advantage of using DSS as an endpoint of prognosis, the above studies have important limitations. None included plasma concentrations of free MTY in a multivariable Cox regression analysis. In addition, HNPGLs were either numerically poorly represented [19–21] and not separately studied in order to assess reliable predictors of disease progression [20,21].

The objective of the present study was, therefore, to assess DSS and potential clinical, genetic and biochemical predictors of progressive disease in a large cohort of patients with PPGLs or HNPGLs, with and without metastases.

2. Methods

2.1. Patients

This study included retrospective data from 989 patients with PPGLs enrolled at seven study centres as detailed in the online Supplement, which contains the expanded methods section. Informed consent was provided by all patients, including written parental consent for those enrolled as children. Among the 989 patients included in the study (Supplementary Tables 1) and 350 patients were excluded from the analysis due to insufficient (<12 months) follow up (Fig. 1). Collected information included the birth date, sex, age at initial tumour diagnosis, the presence of multifocal, recurrent or metastatic disease, location and size of tumours at initial diagnosis, genetics and plasma concentrations of free NMN, MN and MTY (Methods section, Supplement, Fig. S1). Synchronous metastases were defined by the presence of metastases within one year of diagnosis of the primary tumour. Extensive metastatic disease was defined by more than five metastatic lesions and/or the presence of metastases in at least two different organs. Disease-specific death was defined as death due to events that could have been associated with previous long-term or current catecholamine excess (e.g. cardiovascular manifestations), peri- or postsurgical complications, death due to metastatic disease or treatment complications.

2.2. Statistical analysis

Continuous variables are shown as geometric means with confidence intervals of means. A comparison of continuous parameters was performed with the Mann-Whitney U test. Categorical parameters were analyzed using the chi-squared test. The Kaplan-Meier method was applied to estimate DSS and the log-rank test to compare DSS between patient groups. DSS was defined as the time from the date of diagnosis of the primary tumour to the date of disease-specific death or follow up for patients remaining alive. Deaths were recorded until May 2021. Cox proportional hazards regression models with hazard ratios (HR) were evaluated to study the association of clinical, genetic and biochemical parameters with DSS. Cutoffs for continuous parameters were determined by using receiver operating characteristic (ROC) curve analysis and the derived Youden index. Statistical analysis was performed using JMP pro statistical software package version 15. $P < 0.05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

Among the 582 patients in this study with PPGLs, 32.6% developed metastases (Table 1). Patients with metastases were more often males ($P < 0.0001$) and younger

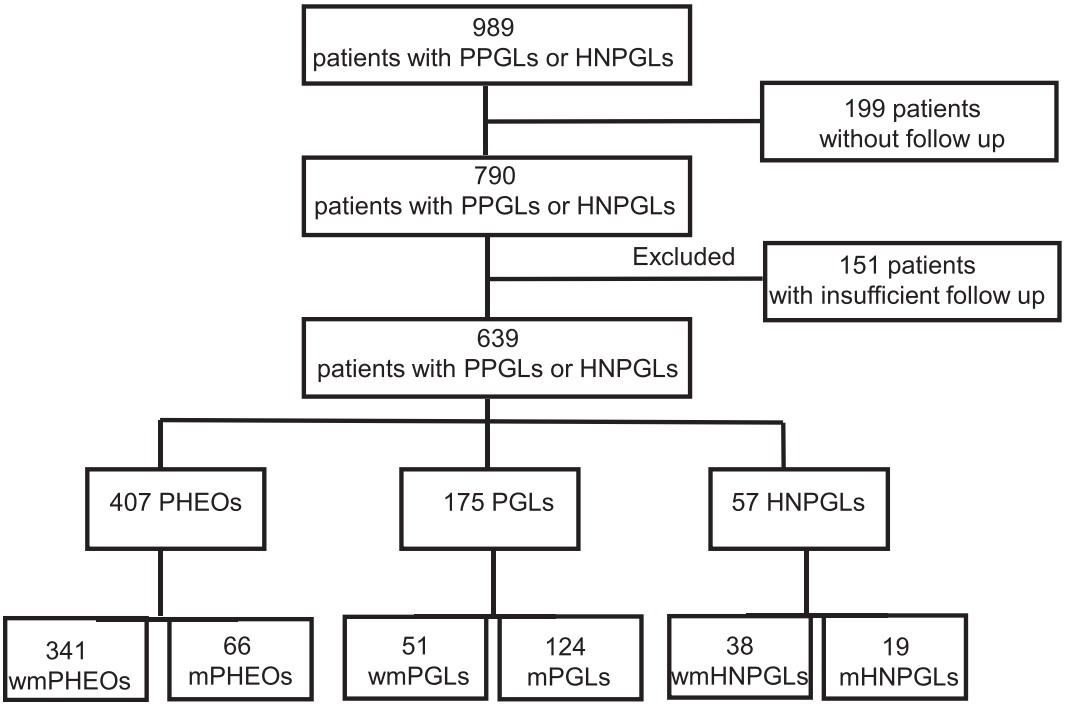


Fig. 1. Flow diagram of patients included in the study. Figure abbreviations: PPGLs: pheochromocytomas and sympathetic paragangliomas, PHEOs: pheochromocytomas, PGLs: sympathetic paragangliomas, HNPGLs: head and neck paragangliomas, wm: without metastases; m: metastatic. DSS: disease-specific survival.

Table 1
Characteristics of patients with PPGLs or HNPGLs.

Characteristics	PPGLs			HNPGLs		
	Without metastases	With Metastases	P Value	Without metastases	With metastases	P Value
Number	392	190		38	19	
Sex (males)	44.6% (175/392)	57.8% (110/190)	0.0010	39.5% (15/38)	42.1% (8/19)	0.5060
Age (years)[a]	42.1 (40.3–43.6)	36.7 (35–38.4)	<0.0001	38 (36.5–39.5)	33.2 (31.6–34.7)	0.2980
Tumour size (cm)[b]	2.8 (2.6–3)	4.7% (4.6–4.8)	<0.0001	1.7 (0.8–2.6)	3.4 (3.35–3.45)	<0.0001
Location (extra adrenal)	13% (51/392)	65.3% (124/190)	<0.0001	–	–	–
Multifocal	6.3% (25/392)	23.6% (45/190)	<0.0001	55.3% (21/38)	47.3% (9/19)	0.2360
Presence of *SDHB* mutation[c]	3.7% (14/369)	47.7% (86/180)	<0.0001	13.1 (5/38)	5.3% (1/19)	0.3970
Recurrence[d]	16.8% (66/392)	73.2% (139/190)	<0.0001	55.2% (21/38)	94.7% (18/19)	<0.0001
Biochemistry (pg/mL)						
Normetanephrine	670 (667–673)	874 (869–879)	0.021	79 (76.6–81.4)	121 (118–124)	0.0990
Metanephrine	157 (152–208)	47.7 (44–51.5)	<0.0001	22.7 (20.7–24.7)	21.0 (18.7–23.2)	0.8990
Methoxytyramine	14.1 (11–17)	48.0 (41.4–54.6)	<0.0001	14.9 (11.7–18.1)	36.4 (25–47.8)	0.5270
Alive	96.4% (378/392)	52.6% (100/190)	<0.0001	100% (38/38)	84.2% (16/19)	0.021
Duration of follow up (years)	5 (2–8)	8 (5–12)	<0.0001	8 (6–10)	10 (7–13)	0.3520

Continuous parameters are shown as geometric means with confidence intervals.
[a] Age at initial tumour(s) diagnosis.
[b] Initial tumour(s) size.
[c] For 23 patients without and 10 with metastases, genetic testing was not available.
[d] Local recurrence and/or new tumours.

($P < 0.0001$) than those without metastases. As expected, the former patients presented more often with larger ($P < 0.0001$), extra-adrenal ($P < 0.0001$), and multifocal tumours ($P < 0.0001$), with higher prevalence of *SDHB* mutations ($P < 0.0001$) and recurrent disease ($P < 0.0001$) than the latter patients, and had more often noradrenergic/dopaminergic tumours with higher concentrations of NMN ($P = 0.0036$) and MTY ($P < 0.0001$) but lower concentrations of MN ($P < 0.0001$). Among the 57 patients with HNPGLs, 33.3% presented with metastases. Patients with metastatic HNPGLs presented more often with larger tumours ($P < 0.0001$) and had a higher prevalence of recurrent disease ($P < 0.0001$) compared to those without metastases.

Patients with either PPGLs or HNPGLs and metastatic disease presented more often with metachronous than with synchronous metastases (Table 2). Interestingly, patients with metastatic PPGLs had a shorter metastatic free interval (4 versus 7 years, $P = 0.0150$) than those with metastatic HNPGLs. Most patients in our cohort presented with an extensive metastatic burden. There were no differences in the sites of metastases between patients with PPGLs versus HNPGLs.

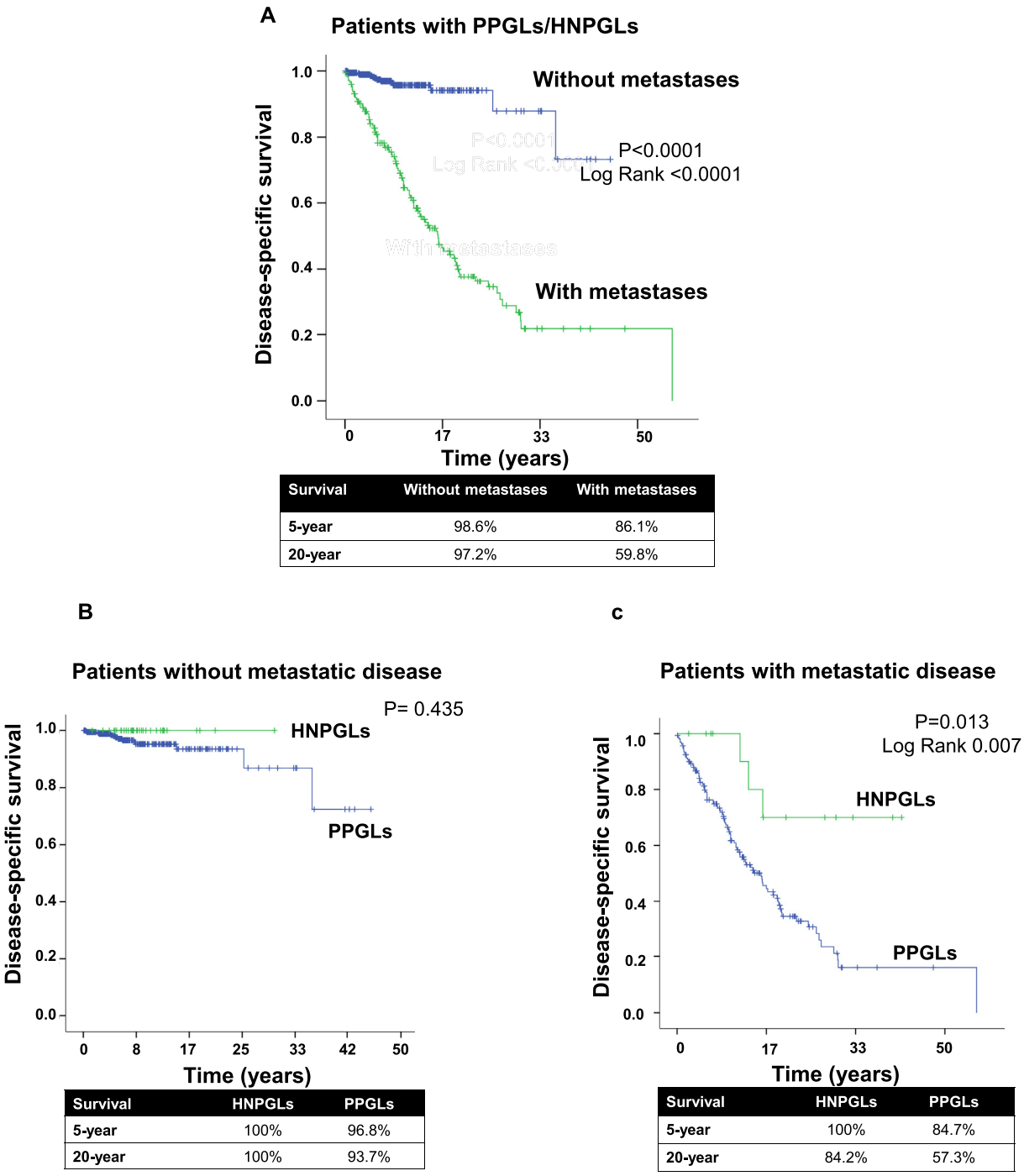
3.2. Disease-specific survival

Patients without metastases and either PPGLs or HNPGLs had an excellent DSS of 40 years (CI:36.9–44), and as expected, longer (LogRank<0.0001, $P < 0.0001$) than those with metastases (22.4 years, CI:18.5–24.3, Fig. 2A). Their median life expectancy was approximately 80 years, similar to the European population (https://ec.europa.eu/eurostat/statistics). All patients with HNPGLs without metastases survived; twenty-year survival rates

Table 2
Specific characteristics of patients with metastatic disease.

Characteristics	Patients with metastatic disease		
	PPGLs	HNPGLs	P Value
	190	19	
Metachronous	64.7% (123/190)	89.4% (17/19)	0.0070
Metastatic free period (years)	4 (1–25)	7 (2–29)	0.0150
Extensive metastases			
>five lesions and/or > two organs	70% (133/190)	78.9% (15/19)	0.2330
Sites of metastases			
Bones	71% (135/190)	73.7% (14/19)	0.4970
Lungs	28.9% (55/190)	47.3% (9/19)	0.0590
Liver	37.8% (72/190)	47.3% (9/19)	0.2960
Lymph nodes	47.8% (91/190)	36.8% (7/19)	0.3120

Continuous parameters are shown as geometric means with confidence intervals.



Survival	Without metastases	With metastases
5-year	98.6%	86.1%
20-year	97.2%	59.8%

Survival	HNPGLs	PPGLs
5-year	100%	96.8%
20-year	100%	93.7%

Survival	HNPGLs	PPGLs
5-year	100%	84.7%
20-year	84.2%	57.3%

Fig. 2. (A) DSS of patients PPGLs/HNPGLs with and without metastases, (B) DSS of patients without metastatic disease: HNPGLs versus PPGLs, and (C) DSS of patients with metastatic disease: HNPGLs versus PPGLs.

for patients with PPGLs without metastases were similarly excellent, reaching 93.7% (Fig. 2B). Among patients with metastases, DSS was significantly longer (33.4 years, CI: 25.3–41.4) for patients with HNPGLs, (LogRank<0.007, $P < 0.0001$) than those with PPGLs (20.2 years, CI:16. 3–24). Specifically, the twenty-year DSS rate for patients with metastatic HNPGLs was 84.2%, compared to 57.3% for patients with metastatic PPGLs (Fig. 2C).

3.3. Predictors of DSS for patients with PPGLs

Univariable analysis (Table 3) revealed that the presence of metastases was the most important determinant of short DSS (HR = 10.2, CI:5.79–17.98, $P < 0.0001$) for patients with PPGLs, followed by larger primary tumour size (HR = 4.5, CI:2.61–7.90, $P < 0.0001$), extra-adrenal location (HR = 3.7, CI:2.47–5.64 $P < 0.0001$), presence

Table 3
Univariable and multivariable cox regression analysis for predictors of DSS for patients with PPGLs.

Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Sex (males)	1.7 (1.18–2.65)	0.0060		
Older age[a]	3.2 (1.89–5.43)	<0.0001	5.4 (2.93–10.29)	<0.0001
Metastatic disease	10.2 (5.79–17.98)	<0.0001	4.8 (2.41–9.94)	<0.0001
Location (extra adrenal)	3.7 (2.47–5.64)	<0.0001	2.6 (1.32–5.23)	0.0007
Larger tumour size[b]	4.5 (2.61–7.90)	<0.0001		
Presence of *SDHB* mutation	3.6 (2.41–5.38)	<0.0001		
Noradrenergic/dopaminergic Phenotype	2.1 (1.51–3.04)	<0.0001		
Normetanephrine[c]	1.7 (1.13–2.55)	0.0100	1.8 (1.12–2.91)	0.0160
Metanephrine[d]	2.1 (1.31–3.09)	<0.0001		
Methoxytyramine[e]	3.2 (2.22–4.84)	<0.0001	1.8 (1.11–2.85)	0.0170

Youden index cutoffs.
[a] Age at initial tumour(s) diagnosis, cutoff 30 years.
[b] Initial tumour(s) size, cutoff 4 cm.
[c] Plasma concentrations of normetanephrine, cutoff 536 pg/mL.
[d] Plasma concentrations of metanephrine, cutoff 60 pg/mL.
[e] Plasma concentrations of methoxytyramine, cutoff 45 pg/mL.

of *SDHB* mutations (HR = 3.6, CI:2.4–5.38, P < 0.0001) and as expected older age at initial diagnosis (HR = 3.2, CI:1.89–5.43, P < 0.0001). A noradrenergic/dopaminergic phenotype (HR = 2.1, CI:1.51–3.04) with higher concentrations of NMN (HR = 1.7, Cl:1.13–2.55, P = 0.0100) and MTY (HR = 3.2, CI:2.22–4.84, P < 0.0001), but lower MN (HR = 2.1, CI:1.31–3.09, P < 0.0001) were associated with shorter DSS. Finally, male sex was associated with 1.7-fold higher risk of disease-specific death (HR = 1.7, CI:1.18–2.65, P = 0.0060) than female sex.

Multivariable analysis (Table 3) showed that the strongest independent factor of a poor prognosis, after older age at initial tumour diagnosis (HR = 5.4, CI:2.93–10.29, P < 0.0001), was the presence of metastases (HR = 4.8, CI:2.41–9.94, P < 0.0001). Interestingly, apart from metastatic disease, extra-adrenal tumour location (HR = 2.6, CI:1.32–5.23, P = 0.0007), higher concentrations of MTY (HR = 1.8, CI:1.11–2.85, P = 0.0170) and NMN (HR = 1.8, CI:1.1–2.91, P = 0.0160) remained independent predictors of poor DSS, whereas larger primary tumour size and presence of *SDHB* mutations did not.

3.4. Predictors of DSS for patients with HNPGLs

Among patients with HNPGLs, the univariable analysis showed that only higher plasma concentrations of MTY were associated with poor DSS (HR = 13, CI:1.35–148, P = 0.0380). Recurrent disease and larger primary tumour size, although more prevalent in patients with metastatic HNPGLs than in those without metastases, showed no association with DSS.

3.5. Predictors of DSS for patients with metastatic PPGLs

Among patients with metastatic PPGLs (Table 4) univariable analysis showed that shorter DSS was as expected associated with older age at initial tumour

Table 4
Univariable and multivariable cox regression analysis for predictors of DSS for patients with metastatic PPGLs.

Variables	Univariable Analysis		Multivariable Analysis	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Older age[a]	4.2 (2.41–7.41)	<0.0001	6.2 (3.2–12.2)	<0.0001
Synchronous metastases	4.7 (2.935–7.71)	<0.0001	4.9 (2.78–8.80)	<0.0001
Larger tumour size[b]	2.1 (1.3–3.2)	0.0020		
Presence of *SDHB* mutation	1.6 (1.04–2.46)	0.0330		
Normetanephrine[c]	2.1 (1.32–3.23)	0.0010		
Methoxytyramine[$]	2.7 (1.8–4.3)	<0.0001	2.4 (1.44–4.14)	0.0010
Extensive metastases[d]	2.1 (1.19–3.64)	0.0100	2.0 (1.07–3.79)	0.0290

Youden index cutoffs.
[a] Age at initial tumor diagnosis, cutoff 30 years.
[b] initial tumour(s) size, cutoff 4 cm.
[c] plasma concentrations of normetanephrine, cutoff 536 pg/mL; plasma concentrations of methoxytyramine, cutoff 45 pg/mL.
[d] Extensive metastases, defined as more than >5 lesions and/or multiorgan metastases.

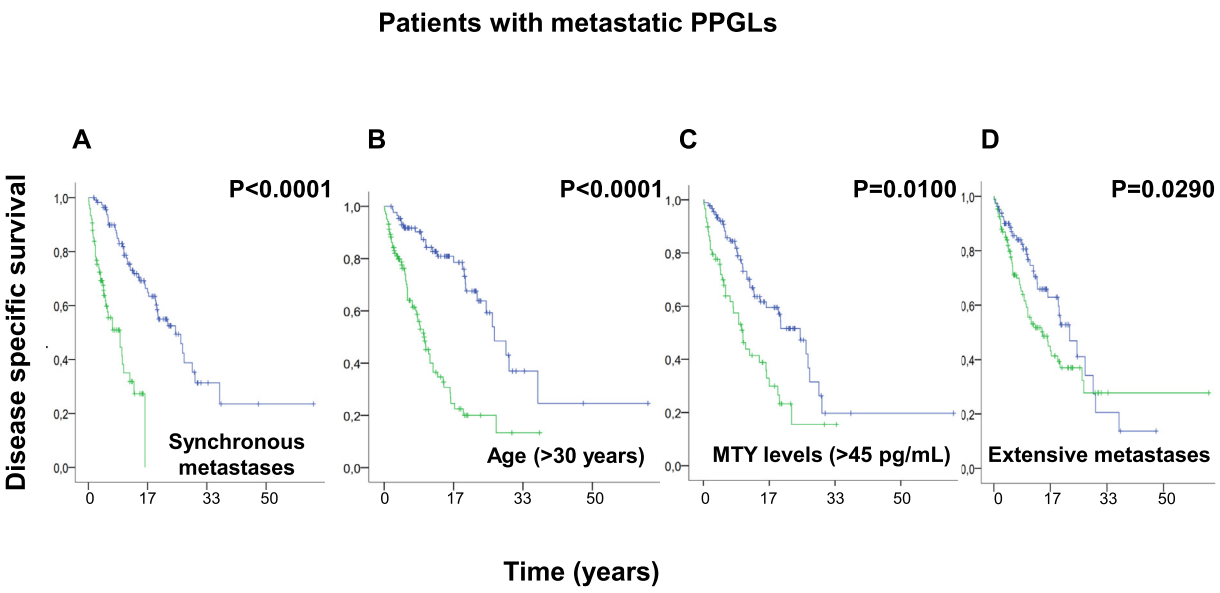


Fig. 3. Predictors of DSS for patients with metastatic PPGLs.

diagnosis (HR = 4.2, CI:2.41–7.41, P < 0.0001). The presence of synchronous metastases (HR = 4.7, CI:2.935–7.71, P < 0.0001), larger primary tumour size (HR = 2.1, CI:1.3–3.2, P = 0.0020), presence of *SDHB* mutation (HR = 1.59, CI:1.04–2.46, P = 0.0330), higher concentrations of NMN (HR = 2.1, Cl:1.32–3.23, P = 0.0010), and MTY (HR = 2.7, CI:1.8–4.3, P < 0.0001), and finally extensive metastatic disease (HR = 2.1, CI:1.19–3.64, P < 0.0100), were also all associated with shorter DSS by univariable analysis. However, multivariable analysis showed that apart from older age at initial tumour diagnosis (HR = 6.2, CI:3.2–12.2, P < 0.0001), only the presence of synchronous metastases (HR = 4.9, CI:2.78–8.80, P < 0.0001), higher concentrations of MTY (HR = 2.4, CI:1.44–4.14, P = 0.0010) and extensive metastatic burden (HR = 2.01, CI:1.07–3.79, P = 0.0290), remained independent predictors of poor DSS (Table 4, Fig. 3). Optimal cutoffs for continuous predictors of DSS are specified in the Results section of the online Supplement.

4. Discussion

The association of tumoural dopamine production with HNPGLs [7], and metastatic disease in patients with PPGLs is well established [5,22–24], whereas until now, it has not been clarified whether this feature also predicts disease progression and shortened survival. The current study not only enlarges on the existing data related to DSS in patients with and without metastatic tumours, but is also the first to establish that high plasma concentrations of MTY are independently associated with poor DSS in patients with metastatic PPGLs, as well as in those with HNPGLs.

Our findings are in contrast to the study of Hamidi *et al.* [20], where dopaminergic tumour phenotype failed to remain an independent predictor of DSS in the multivariable analysis. The discrepancy likely relates to the fact that in that particular study [20], the authors used urinary dopamine to assess the dopaminergic phenotype. However, almost all dopamine in urine is derived from renal uptake and decarboxylation of circulating L-dopa [25,26], and therefore, provides a poor marker of tumoural dopamine production [7]. MTY in urine is similarly derived from sources that are largely independent of the circulating MTY [27], and thus also provides a poor biomarker of tumoural dopamine production compared to measurements in plasma [6,28].

The association of a dopaminergic phenotype with poor survival in patients with metastatic PPGL likely reflects the undifferentiated nature of the tumours and the association of this with the activation of pseudohypoxia pathways [29]. These pathways impact the invasion-metastasis cascade, leading to more extensive and rapidly progressing metastasis [30,31]. Moreover, it seems that both hypermethylation and activation of pseudohypoxia pathways synergistically drive the mesenchymal transition step in metastasis [32,33]. Since hypermethylation also leads to the silencing of genes that otherwise contribute to the more differentiated nature of chromaffin cell tumours [34], it seems likely that both this and pseudohypoxia pathway activation may underlie the association of the undifferentiated dopaminergic phenotype with poor survival in patients with metastatic PPGLs.

We further demonstrate that a presentation of synchronous metastases and extensive metastatic disease is associated with poor DSS in patients with metastatic

PPGLs. The former finding is in agreement with Hamidi *et al.* [20], although this and the latter finding contrasts with the study of Hescot *et al.* [21], where synchronous metastases and tumour burden did not emerge as independent prognostic markers of poor DSS. The latter discrepancy could be partially explained by the different definitions of extensive disease and limited imaging of metastatic disease (only 58%) in the study of Hescot *et al.* [21]. The association of poor DSS with the synchronous disease might be explained by heterogeneous patterns of genomic changes that occur in synchronous versus metachronous neuroendocrine tumours [35] and may impact not only metastatic progression [36,37] but also survival.

Although, as expected, patients with metastases presented with shorter DSS compared to those without, the progression of the disease and life spans were highly variable. Until now, clinical evidence on how to stratify and treat patients with metastases is limited. Current treatments and therapeutic interventions are considered only among patients with symptoms of catecholamine secretion, high tumour burden or progressive disease [38]. In this direction, others have suggested the consideration of outcome markers focused on genomic alterations [39]. Similarly, our findings are also relevant for the stratification, management and treatment of patients with metastatic PPGLs. In particular, apart from the high tumour burden, the presence of synchronous metastases or higher plasma concentrations of MTY could be used to identify patients who might benefit from intensified management and therapeutic interventions, independent of the need to assess the rate of disease progression.

In contrast to previous studies [15,19], the multivariable analysis of our study revealed no significant association of *SDHB* mutations with DSS for patients with or without metastatic PPGLs. Although this might seem surprising, these findings may be explained by shared characteristics of *SDHB*-mutated-tumours with the larger proportion of other tumours likely to show a metastatic progression or poor DSS. Thus, with multivariable analysis, the associations of *SDHB* mutations with DSS observed with univariable analysis are nullified by more prevalent variables, such as higher plasma concentrations of MTY. However, the fact that patients with *SDHB* mutation were significantly younger than those without (results section, supplemental appendix) may have downgraded the dominance of the *SDHB* mutation status in the multivariable analysis, as younger age is a well-established independent predictor of longer DSS. Similarly, the multivariable analysis of our study revealed no significant association of the size of primary tumours with the DSS among patients with metastatic PPGLs. This is in contrast with the study of Hamidi *et al.* [20]; however, in that study, patients with HNPGLs tumours were included in the same multivariable analysis, which might have overestimated the importance of tumour size as a predictor of DSS in the overall population.

The present finding of an inverse association between plasma MTY with DSS is also relevant to the management of patients with HNPGLs. Until now, 'watchful waiting' is suggested for 'non-functional' HNPGLs, especially for those without evidence of significant tumour growth or compression of surrounding structures [40]. The poor DSS in patients with HNPGLs associated with high plasma MTY concentrations mainly reflect their higher risk of developing metastases [5]. In these particular cases, resection of the tumour at an earlier stage may provide a more appropriate approach for reducing the risk of metastases and minimizing mortality than 'watchful waiting'. Similarly, among patients with PPGLs, apart from the presence of metastases, the presence of extra-adrenal tumours, high plasma concentrations of NMN and MTY emerge as prognostic parameters of poor DSS, and patients with these characteristics might benefit from more intensified management and follow-up programs.

Our study has limitations, including possible referral bias and a lack of reliable and complete data regarding the treatment of patients with metastases (see Discussion section of the online Supplement). Despite the limitations, our study has unparalleled strengths. We were able to retrieve full and comprehensive clinical, genetic and biochemical data from one of the largest cohorts of patients reported to date with either PPGLs or HNPGLs, including those with and without metastases. Importantly, plasma concentrations of free MTY were for the first time included as possible predictors of DSS in a multivariable analysis. In addition, we examined patients with HNPGLs separately due to their different origin, presented as expected with different characteristics, different rates and predictors of DSS than those with PPGLs. Finally, the long duration of follow-up should be mentioned, a study strength that minimized the possibility of misclassifying patients with metastatic potential among those without evidence of metastases.

5. Conclusion

This study establishes that higher plasma concentrations of MTY and the presence of synchronous or extensive metastatic disease are associated with poor DSS among patients with metastatic PPGLs. In contrast, among patients with HNPGLs, only high plasma concentrations of MTY are associated with shorter DSS. These predictors should be considered in the individualized management and follow-up strategies of patients with PPGLs and or HNPGLs.

Author contributions

C.P, K.P., J. W.M. L., and G.E. contributed to the conception and design of the study, analyzed the data, drafted and revised the paper; **T.P., L.M., A.M.B., G.C.,**

F.B., H.R., A.J., H.J.L.M., contributed to the enrollment of patients in the study, selection of samples, collection and interpretation of clinical data and revised the paper; **M.N.K., D.T., M.R.,** drafted and critically revised the paper; all authors approved the final version of the manuscript.

Data availability

The data generated in this study are available upon request from the corresponding author.

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Conflict of Interest statement

The authors declare that they have no financial relationships that could be broadly relevant to the work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2022.03.032.

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