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Original research

Quality of life in patients with pheochromocytoma and paraganglioma: influence of tumor type, genetics and surgical resection

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Abstract

Context **Pheochromocytomas and paragangliomas (PPGL) are rare endocrine tumors with high heritability. Carriers of pathogenic variants (PVs) in susceptibility genes face a lifelong risk of recurrence or metastatic disease. Quality of life (QoL) in patients with PPGL, a history of PPGL and PV carriers, remains insufficiently studied.**

Methods **We assessed patient-reported QoL in patients with PPGL before and after surgery and in carriers of susceptibility PVs for the development of PPGLs within the prospective *ProsPheo* study. QoL was evaluated using standardized questionnaires (SF-12, PHQ-D, and GAD-7).**

Results **A total of 202 participants were analyzed. SF-12 physical component summary scores (PCS) differed significantly across subgroups ($P = .006$), with the lowest PCS scores in patients with metastatic PPGL (40.3) and unresected head and neck paragangliomas (HNPGL) (40.0), compared with PV carriers after curative PPGL resection (50.2). Within metastatic disease, hormonally active tumors showed lower PCS scores than inactive tumors (36.9 vs 46.2; $P = .03$). Perceived physical health in carriers of a PV without history of a PPGL was significantly lower compared to the age-matched general population. Mental health was not significantly impaired across all subgroups. Clinically relevant anxiety was reported in 15.2% of PV carriers and 21.7% of patients with unresected HNPGLs, compared with about 5.9% in the general population.**

Conclusions **Patient-reported physical health was reduced in patients with metastatic PPGLs, unresected HNPGLs, and PV carriers without prior PPGL, whereas patients after curative PPGL resection reported QoL comparable to the general population, regardless of PV status, suggesting that annual follow-up has minimal impact on QoL.**

Keywords PPGL, quality of life, anxiety, HNPGL

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Significance

Patients with pheochromocytoma and paraganglioma (PPGL) and carriers of pathogenic variants (PVs) in susceptibility genes for PPGLs face a lifelong risk of recurrent or new PPGLs. However, data on quality of life (QoL) remain limited. In this prospective multicenter study, we assessed QoL in patients with resected and metastatic PPGLs and in PV carriers without prior PPGL.

QoL was reduced in patients with metastatic PPGLs, with unresected head and neck paragangliomas, and in PV carriers without prior PPGL, whereas patients after curative surgery, independent of PV status, reported a QoL comparable to the general population. These findings suggest that most patients with curatively resected PPGLs maintain good physical and mental health, and structured follow-up does not appear to compromise QoL.

Introduction

Pheochromocytomas and paragangliomas (PPGL) are rare neuroendocrine neoplasms that arise from the adrenal medulla (pheochromocytoma/intra-adrenal paraganglioma) or from extra-adrenal paraganglia of the sympathetic or parasympathetic nervous systems (paraganglioma).[1,2] Metastatic disease occurs in approximately 10% to 15% of patients with pheochromocytomas and 35% to 40% of patients with paraganglioma at initial diagnosis or during follow-up.[1,3] Among patients with PPGL, 30% to 35% harbor germline pathogenic variants (PVs), whereas another 35% to 40% possess somatic PVs.[4,5] Catecholamine secretion, a characteristic feature of functionally-active PPGL, may lead to symptoms including headaches, hypertension, hyperhidrosis, nausea, and palpitations.[6-8] The first-line treatment of non-metastatic PPGL is surgical resection.[9,10] Despite complete resection, patients with a history of PPGL remain at a lifelong elevated risk for developing recurrent PPGL.[6,10,11] Carriers of susceptibility PVs for PPGL, such as *SDHB*, are at higher risk to develop a recurrence of PPGL or metastatic disease throughout their lifetime.[12] Currently, no reliable biomarkers exist for predicting metastatic disease.[9,13-15] Hence, the diagnosis of a PPGL, particularly in PV carriers, has lifelong implications for patients. However, our understanding of the long-term effect of PPGL on physical and mental health remains limited. A few studies focusing on cardiometabolic outcomes in patients with resected PPGL have reported higher blood pressure, persistent cardiac dysfunction and dysglycemic regulation, and increased body mass index, post-tumor removal compared to healthy controls.[16-19] However, the long-term effect on patient-reported quality of life (QoL) in PPGL patients is largely unknown. In patients with other neuroendocrine neoplasms, reports on QoL are heterogenous but, compared to other cancers, in general QoL is relatively preserved.[20-22] In contrast, earlier studies in patients with PPGL reported a decreased QoL compared with their own controls after resection of the PPGL and controls from the general population.[23-25] Limited data on QoL in patients with PPGL render it difficult for clinicians to provide adequate psychosocial support during their, often life-long, follow-up. Furthermore, individuals with hereditary syndromes or metastatic disease may experience additional psychological burden, adversely impacting both physical and mental well-being. To address this gap, we conducted a comprehensive assessment of QoL within our well-characterized cohort from an ongoing international prospective multicenter study.

Methods

Study population

For this study, we analyzed subjects enrolled in the prospective "Multicenter Evaluation of Pheochromocytoma and Paraganglioma Diagnostic Testing, Subdifferentiation, Therapy, Outcome and Genetics," referred to as the "*ProsPheo*" study (NCT03344016), in Zurich, Switzerland and Würzburg and Dresden, Germany. Participants enrolled in the *ProsPheo* study are either newly diagnosed with a PPGL, have a metastatic PPGL, have a history PPGL, or are carriers of genetic PVs predisposing them to develop a PPGL. A total of 247 participants were extracted from the study database between April and June 2025. Out of the original cohort of 247 patients, 45 patients were excluded due to missing data. Consequently, the results of 202 participants with complete data available from at least one of the questionnaires were analyzed as part of this study.

Metastatic PPGL was defined by the presence of distant metastases in locations where chromaffin cells are not physiologically present.[1] Measurements of height, weight, and current medications, were assessed with the concurrent visit and filling out of the questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by the square height in meters (kg/m^2). The presence of other tumors was documented by the treating physician. Participants that agreed to germline testing received germline sequencing at their local centers. The genes covered were *SDHA, SDHAF2, SDHB, SDHC, SDHD, VHL, TP53, NF1, RET, TMEM127, MAX, MET,* and *FH*.[13]

This study was conducted in accordance with the principles of the Declaration of Helsinki and adhered to the laws and regulations of the Ethics Commission of the Canton of Zurich. Written informed consent was obtained from all participants. The *ProsPheo* study was approved by the local ethics committees of Dresden (EK 210052017), Würzburg (129/19), and Zurich (BASEC 2017-00963).

Assessment of QoL

Patient-reported QoL was evaluated using standardized self-administered questionnaires completed by participants at baseline (study inclusion) and during annual follow-up visits at the study center. The 12-item Short Form Health Survey (SF-12), a validated abbreviated version of the SF-36, was employed to assess health-related QoL.[26] The SF-12 assesses the patients subjective views on physical functioning, emotional well-being, pain, and social interactions, from which summary scores for physical and mental components (PCS and MCS) are calculated.[26-28] Higher scores indicate better perceived health and fewer health-related complaints.[27,29]

Depression was assessed using the German version of the short version of the Patient Health Questionnaire (PHQ-D).[30,31] A diagnosis of *Major Depressive Syndrome* was made if 5 or more of items 1a-i were endorsed as occurring "more than half the days," with at least one being item 1a or 1b (item 1i was also considered if endorsed as "several days"). *Any Depressive*

Syndrome was defined by the endorsement of 2 to 4 such items, again requiring that either item 1a or 1b be included.[30,32]

Anxiety symptoms were assessed using the German version of the Generalized Anxiety Disorder 7-item scale (GAD-7), a validated screening tool to identify symptoms of generalized anxiety disorder as defined by the DSM-IV.[33] Symptom frequency over the past 2 weeks is rated on a 4-point scale (0 = not at all to 3 = nearly every day) by the study participant, and a total score then calculated (range: 0–21).[33] In line with Andersen, a cut-off score of ≥10 was used to categorize participants as with clinically relevant anxiety.[34] The Epworth Sleepiness Scale was used to evaluate subjective daytime sleepiness.[35] The summed score reflects overall daytime sleepiness, with scores ≥10 indicating excessive sleepiness.

Statistical analysis

Questionnaires with missing responses were excluded from their respective analyses.

Categorical variables were compared using Pearson's chi-square test or McNemar's test, as appropriate. Continuous variables were assessed for normality using the Shapiro–Wilk test and visual inspection. For normally distributed data, group comparisons were performed using one-way ANOVA with Tukey's post hoc test. For non-normally distributed data, the Kruskal–Wallis test was used. Independent-samples or paired-samples *t*-tests were used to compare continuous variables between study groups or within subjects before and after PPGL resection, as appropriate. Z-scores for individual patients were calculated with the age-specific German population means. For patients younger than 18 years old, the mean of the age group 18-24 years was used. One-sample *t*-tests were used to test whether the mean z-scores of subgroups differed from the age-matched population.

All statistical tests were 2-sided, with a significance level set at $P < .05$. Statistical analyses were conducted using the open-source statistics software R (version 4.3.2, R Foundation for Statistical Computing).[36]

Results

Patient characteristics

This study included 202 patients from the *ProsPheo* cohort. Of these, 33 patients (16.4%) were carriers of pathogenic variants (PVs) in susceptibility genes without a history of PPGL, 20 patients (9.9%) had metastatic PPGL, and 149 patients (73.8%) were enrolled at the time of initial PPGL diagnosis or during follow-up after surgical resection. We defined 4 subgroups for comparison (Table 1): (i) pathogenic-variant (PV) carriers without a history of PPGL, (ii) patients with metastatic PPGL, (iii) patients who underwent complete resection of a pheochromocytoma or thoraco-abdominal paraganglioma (PGL) and remained recurrence-free for ≥6 months, and (iv) patients with head and neck PGL (HNPGL).

Subgroups were further stratified as follows: resected PPGL (iii) into known PV carriers (iiia) verus non-carriers (iiib, negative or absent genetic testing, sporadic PPGL); and HNPGL into resected (iva) versus non-resected (ivb) cases. For groups (iii) and (iva), only patients with a QoL assessment ≥6 months after surgery were included to avoid transient post-operative effects on QoL.

Table 1 Characteristics of the study subgroups.

	PV carrier without history of PPGL (i)	Metastatic PPGL (ii)	History of Pheo or abdominal/thoracic PGL (>6 months after PPGL resection)		HNPGL		*P*-value
			PV carriers (iiia)	No PV known/ not tested (iiib)	Resected (iva)	Unresected (ivb)	
Number of patients in total	33	20	18	33	8	24	
Age, median (Q1, Q3)	39 (31, 56)	53 (43, 60)	33 (26, 54)	57 (47, 61)	49 (45, 56)	61 (47, 67)	<.001
Sex, F	17 (51.5%)	7 (35%)	12 (66.7%)	19 (57.6%)	6 (75%)	17 (70.8%)	.16
BMI, mean (SD)	24.9 (4.4)	25.6 (3.6)	26.6 (5.1)	28.4 (6.2)	25.8 (2.9)	24.7 (5.7)	.05
Number of patients with pheochromocytoma	0 (0%)	13 (65%)	14 (77.8%)	29 (87.9%)	0 (0%)	1 (4.2%)	<.001
Number of genetic carriers	33 (100%)	11 (55%)	18 (100%)	0 (0%)	8 (100%)	9 (37.5%)	
Number of patients with *SDHB*-related PV	12 (36.4%)	8 (40%)	5 (27.8%)	0 (0%)	4 (50%)	6 (25%)	.002
Median time since surgery (Q1, Q3) in months	—	69 (17, 143)	84 (29, 225)	61 (39, 95)	148 (75, 283)	—	.05
Hormone-active at time of assessment	—	13/20 (65%)	—	—	—	8/24 (33%)	
Presence of other (non-PPGL) tumors	7 (21.2%)	0 (0%)	3 (16.7%)	5 (15.2%)	0 (0%)	7 (29.2%)	.36

Abbreviations: HNPGL: head and neck paraganglioma; PGL: paraganglioma; Pheo: pheochromocytoma; PV: pathogenic variant.

If multiple assessments were available, the first assessment closest to the 1-year mark was used.

Patients with PVs in susceptibility genes were significantly younger than the other subgroups. Median age was 39 years in PV carriers without a history of PPGL (group i) and 33 years in PV carriers with a resected PPGL (group iiia). In contrast, the median age was higher in patients with metastatic disease (group ii, 53 years) and in those followed after PPGL resection without a known PV (group iiib, 57 years).

The proportion of patients carrying PVs in the *SDHB* gene was highest in the group of resected HNPGLs (group iva, 4/8; 50%) and in the metastatic disease group (8/20; 40%). A high proportion of PV carriers without PPGL (7/33; 21.2%) had other non-PPGL tumors, including breast cancer, rectal cancer, medullary thyroid carcinoma, neurofibromas, differentiated thyroid cancer, brain cancer, and other neuroendocrine tumors.

Physical (PCS) and mental (MCS) health scores

The 4 groups and their subgroups were examined for differences in QoL using the SF-12 physical and mental component summary scores (PCS and MCS) and the GAD-7 questionnaires to identify a generalized anxiety disorder as well as the short version of the PHQ for the assessment of depression (Table 2).

The mean PCS score differed significantly between groups ($P = .006$), with the lowest scores observed in patients with metastatic PPGL (group ii, mean PCS 40.3) and patients with unresected HNPGLs (group ivb, mean PCS 40.0) compared to PV carriers with resected PPGL (group iiia, mean PCS 50.2, $P = .015$ resp. $P = .007$ after post-hoc testing) (Figure 1). To further investigate the patients with metastatic PPGLs (ii), we separately assessed hormone-active versus hormone-inactive tumors (Table 3). Patients with hormone-active, catecholamine-secreting disease reported markedly lower physical functioning (PCS 36.9) compared to those with hormone-inactive disease (PCS 46.2; $P = .03$, Table 3).

Consistent with the pattern observed for physical health, mental health was impaired in patients with metastatic PPGLs (group ii, mean MCS overall 44.4). The mean MCS score of the SF-12 was again lower in the metastatic group with catecholamine-secreting tumors (mean MCS 40.3) compared to non-secreting metastatic PPGLs (mean MCS 51.5, n.s.: $P = .07$). However, overall, no significant differences in mental health across groups were observed.

To account for age-related impact on physical and mental health, individual PCS and MCS values were converted to age-adjusted z-scores using the corresponding reference age group reported for the German reference population in a SF-12 validation study.[37] A negative z-score indicates worse health status than expected for an individual of the same age in the general population.

In the group of genetic carriers without a history of PPGL (group i), the mean PCS z-score was −0.89 (95% CI −1.33 to −0.45), indicating worse physical health compared with the age-matched general population (Table 4, Figure 2). Similarly, the group of unresected HNPGLs (ivb) had a significantly lower physical health, compared to the age-matched general population (PCS z-score −0.83, 95% CI −1.25 to −0.40). Patients with metastatic disease (group ii) were also below age-matched general population, with the lowest z-score of all groups (PCS z-score −1.02, 95% CI −1.67 to −0.38), whereas all other groups showed no significant impairment of their physical health compared to an age-matched general population[37] (Table 4, Figure 2).

No significant differences in mental health compared to the age-matched general population were found across groups but with patients with metastatic PPGLs (group ii) showing the greatest reduction in mental health compared to the age-matched group (mean MCS z-score −0.59, 95% CI −1.19 to 0.02) (Table 4). Mean MCS z-scores were not significantly different from the age-matched general population for PV carriers without PPGLs (group i), patients with a history of resected PPGL with and without known PV (groups iiia and iiib) and patients with resected or unresected HNPGL (group iva and ivb), suggesting no relevant mental health impairment in these groups that frequently face lifelong follow-up.

Anxiety and depression

Anxiety symptoms, assessed using the GAD-7, with a cut-off score ≥10, were descriptively more frequent across all groups except the group of resected HNPGLs (group iva) compared to the general German population (oveall 5.9%).[38,42] Clinically relevant anxiety was reported in 16.7% of PV carriers with a history of resected PPGL (group iiia) and 15.2% of PV carriers without history of a PPGL (group i) and 21.7% of patients with unresected HNPGLs (group ivb). Presence of any depression, as evaluated by the German version of the short version of the Patient Health Questionnaire (PHQ-D), was comparable to the general German population. However, the self-reported prevalence of depressive symptoms and the use of psychotropic medication were unexpectedly low among genetic carriers without a history of PPGL (i) in comparison to reference data from the general population[39] (Table 2). No differences in quality of sleep as assessed by the Epworth Sleepiness Scale were found between the patient groups.

Discussion

Within the framework of the ongoing prospective *ProsPheo* registry study, we compared patient-reported QoL across different subgroups of patients with PPGLs and carriers of PVs in susceptibility genes associated with the development of PPGL. Physical health as determined by the SF-12 was significantly impaired in the sub-group of patients with unresected HNPGLs and metastatic PPGLs, especially those with catecholamine-secreting tumors, as compared to patients with a known PV in a susceptibility gene for the development of PPGLs and history of a previous, resected PPGL (group iiia). In contrast, no significant changes in perceived mental health as assess by the SF-12 were found across groups.

Age is a major determinant of self-reported physical and mental health, and the PV carriers were significantly younger than the other subgroups. To account for this, we converted PCS and MCS values into age-adjusted z-scores using the corresponding age-related data from the German reference population.[37] We observed significantly impaired perceived physical health in patients with unresected HNPGLs, those with metastatic disease, and notably, in patients with a PV in a susceptibility gene

Table 2 Results of questionnaire-based QoL assessment.

	PV carrier without history of PPGL (i)	Metastatic PPGL (ii)	History of Pheo or abdominal/thoracic PGL (>6 months after PPGL resection)		HNPGL		*P*-value	*Age-group related values (in brackets) from the general German population*[37-41]
			PV carriers (iiia)	No PV known/ not tested (iiib)	Resected (iva)	Unresected (ivb)		
SF-12 mean PCS (SD) *N: 32, 19, 16, 30, 6, 23*	45.0 (7.4)	40.3 (9.3)	50.2 (8.9)	45.5 (10.1)	43.1(14.6)	40.0 (5.9)	.006	35-44 (52.95, 8.02) 45-54 (50.28, 8.88) 55-64 (46.29, 9.80)
SF-12 mean MCS (SD) *N: 32, 19, 16, 30, 6, 23*	51.9 (9.6)	44.4 (13)	46.4 (11.4)	47.0 (12.7)	45.4 (11.9)	50.6 (12.1)	.22	35-44 (49.27, 9.67) 45-54 (49.57, 9.79) 55-64 (51.18, 10.14)
Number of patients with Epworth scale score >10	7/33 (21.2%)	1/18 (5.6%)	6/18 (33.3%)	4/30 (13.3%)	3/8 (37.5%)	4/23 (17.4%)	.23	
Number of patients with a GAD-7 score >10	5/33 (15.2%)	3/19 (15.8%)	3/18 (16.7%)	5/31 (16.1%)	0/8 (0%)	5/23 (21.7%)	.85	35-44 (5%) 45-54 (1.7%) 55-64 (3.7%) Overall 5.9%
Mean GAD-7 score (SD) *N: 32, 19, 18, 31, 8, 23*	4.8 (4.7)	5.8 (5.1)	4.7 (4.6)	5.5 (4.4)	3.6 (2.9)	5.6 (4)	.81	<40 (M: 2.92, F: 3.9) 50-54 (M: 3.0, F: 4.11) 55-59 (M: 3.24, F: 4.59)
Number of patients with presence of any depression based on PHQ	3/33 (9.1%)	5/18 (27.8%)	3/18 (16.7%)	5/31 (16.1%)	1/8 (12.5%)	3/23 (13%)	.67	35-44 (13.8%) 45-54 (20.3%) 55-59 (22.3%)
Number of patients on psychotropic medication (questionnaire, self-reported)	1/33 (3%)	1/18 (5.6%)	2/18 (11.1%)	6/32 (18.8%)	1/8 (12.5%)	0/24 (0%)	.11	

Sample sizes (N) differ between questionnaires due to missing data. Group-specific N is indicated for each row where applicable.
Abbreviations: GAD-7: Generalized Anxiety Disorder 7-item scale; HNPGL: head and neck paraganglioma; MCS: Mental Component Summary; PCS: Physical Component Summary; PGL: paraganglioma; Pheo: pheochromocytoma; PHQ: Patient Health Questionnaire; PV: pathogenic variant; SF-12: 12-Item Short Form Survey.

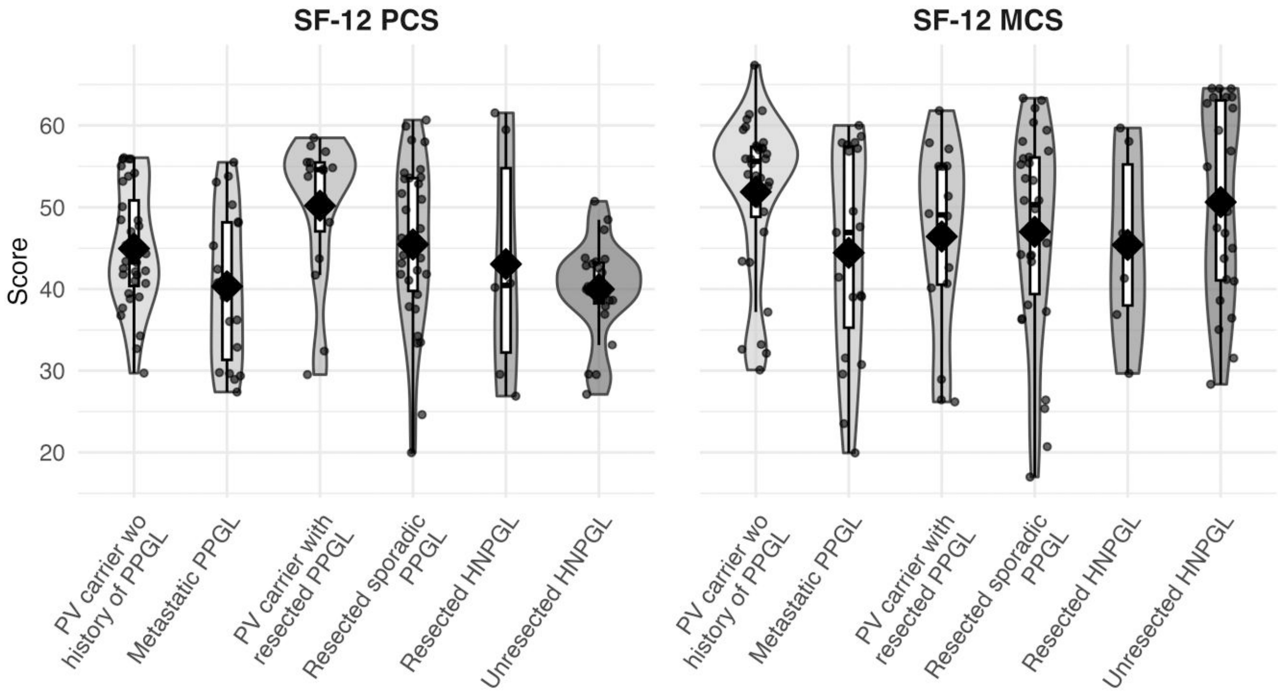

Figure 1 Violin plot illustrating the distribution of patient-reported QoL scores among patients with metastatic PPGL, patients with a history of PPGL and PV carriers without PPGL. Scores shown include the physical and mental component summaries of the SF-12 questionnaire (SF-12 PCS, SF-12 MCS). Each violin plot represents the complete distribution of scores, with embedded boxplots indicating median and interquartile range. Black diamonds indicate group means and black dots show individual patient values. Abbreviations: Pheo: pheochromocytoma; PGL: paraganglioma, HNPGL: head and neck paraganglioma; PV: pathogenic variant; wo: without; SF-12: 12-Item Short Form Survey; PCS: Physical Component Summary; MCS: Mental Component Summary.

Table 3 Results of questionnaire-based QoL assessment in patients with hormone-active versus hormone-inactive metastatic PPGLs.

	Hormone-active metastatic PPGL	Hormone-inactive metastatic PPGL	*P*-value
Number of patients in total	13	7	—
Age, median (Q1, Q3)	50 (38, 55)	60 (54, 64)	.1
Sex, F	3 (23.1%)	4 (57.1%)	.18
BMI, mean (SD)	26.4 (4.0)	24.3 (2.2)	.21
Number of patients with pheochromocytoma	10/13 (76.9%)	3/7 (42.9%)	.17
Number of PV carriers	7 (53%)	4 (57%)	1.00
Number of patients with *SDHB*-related PV	5 (38.5%)	3 (42.9%)	1.00
Median time since surgery (Q1, Q3) in months	69 (15, 167)	60 (34, 79)	.62
Presence of other (non-PPGL) tumors	0	0	—
SF-12 mean PCS (SD)	36.9 (8)	46.2 (9.1)	.03
SF-12 mean MCS (SD)	40.3 (13.1)	51.5 (9.9)	.07
Number of patients with a GAD-7 score >10	3/12 (25%)	0/7 (0%)	.26
Mean GAD-7 score (SD)	7.8 (5.2)	2.6 (3.1)	.03
Number of patients with presence of any depression based on PHQ	4/11 (36.4%)	1/7 (14.3%)	.6
Number of patients on psychotropic medication (questionnaire, self-reported)	1/11 (9.1%)	0/7 (0%)	1.00

Abbreviations: GAD-7: Generalized Anxiety Disorder 7-item scale; MCS: Mental Component Summary; PCS: Physical Component Summary; PHQ: Patient Health Questionnaire; PV: pathogenic variant; SF-12: 12-Item Short Form Survey.

Table 4 Age-standardized PCS and MCS z-scores by clinical subgroup.

		Age-standardized PCS z-score			Age-standardized MCS z-score		
	N	Mean	95% CI	*P*-value	Mean	95% CI	*P*-value
PV carrier without history of PPGL (i)	32	−0.89	−1.33 to −0.45	<.001	0.20	−0.17 to 0.56	.27
Metastatic PPGL (ii)	19	−1.02	−1.67 to −0.38	.004	−0.59	−1.19 to 0.02	.06
PV carriers with resected Pheo or abdominal/thoracic PGL (iiia)	16	−0.38	−0.98 to 0.21	.19	−0.31	−0.95 to 0.33	.32
No PV known/not tested with resected Pheo or abdominal/thoracic PGL (iiib)	30	−0.20	−0.60 to 0.20	.32	−0.36	−0.83 to 0.11	.13
Resected HNPGL (iva)	6	−0.70	−2.28 to 0.89	.31	−0.49	−1.69 to 0.72	.35
Unresected HNPGL (ivb)	23	−0.83	−1.25 to −0.40	<.001	−0.01	−0.51 to 0.49	.97

A negative z-score indicates worse health status than expected for an individual of the same age in the general German population.
Abbreviations: HNPGL: head and neck paraganglioma; MCS: Mental Component Summary; PCS: Physical Component Summary; PGL: paraganglioma; Pheo: pheochromocytoma; PV: pathogenic variant; SF-12: 12-Item Short Form Survey.

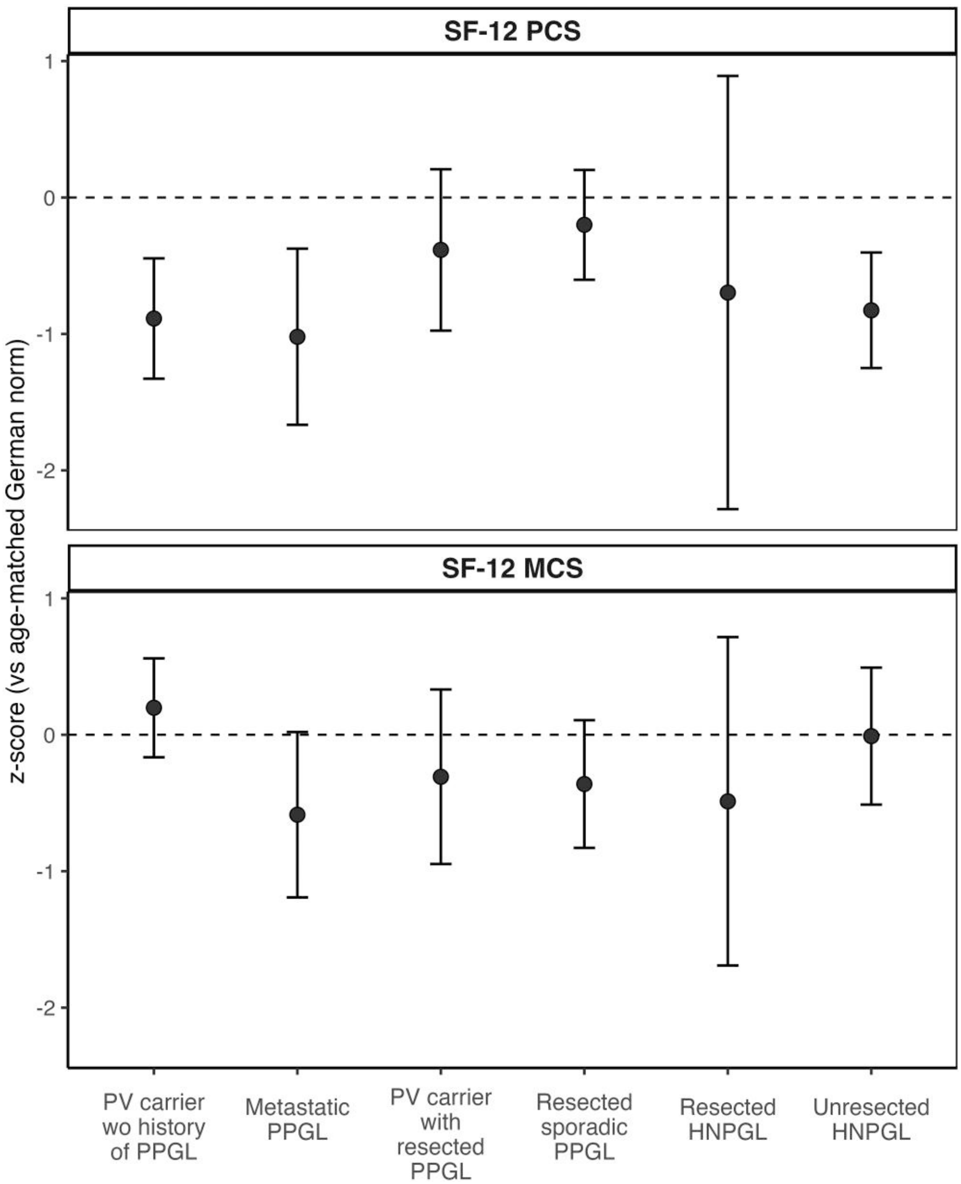

Figure 2 Age-standardized PCS and MCS z-scores by clinical subgroup. Points represent group means and error bars indicate 95% confidence intervals. A negative z-score indicates worse health status than expected for an individual of the same age in the general German population. Abbreviations: PPGL: pheochromocytoma and paraganglioma; HNPGL: head and neck paraganglioma; PV: pathogenic variant; wo: without.

predisposing to a PPGL who have not yet developed a PPGL (group i). Interestingly, the mental health of the last group was not impaired compared to the age-related general population. Additionally, patients with a PV in a susceptibility gene who already had a PPGL resected (group iiia) did not have significantly lower physical or mental health compared to the age-related general population. One possible explanation is that other comorbidities or non-PPGL tumors related to the PV negatively impact physical health.

In patients with resected PPGLs who were free of disease at the time of assessment, we did not observe major impairments in mental or physical health, as measured by the SF-12, nor elevated self-reported symptoms of depression. Hence, a history of a curative surgically resected, potentially metastatic cancer, did not appear to negatively impact long-term QoL in our cohort independent of PV carrier status. Given that most patients in the *ProsPheo* cohort undergo regular follow-up with clinical assessments, biochemical testing, and imaging to monitor for recurrence, our data suggest that this surveillance does not negatively impact mental health-related QoL.

We report reduced self-reported physical health in patients with metastatic PPGLs, with the lowest PCS scores in those with hormonally-active, catecholamine-secreting tumors. This pattern underscores the clinical relevance of catecholamine-related symptom burden as a determinant of functional status and supports prioritizing symptom control in the management of metastatic disease. Patients with metastatic disease also reported lower mental health determined by the SF-12 compared to a similar age group from the general German reference population (mean MCS z-score −0.59, 95% CI −1.19 to 0.02).[37,40] This is consistent with previous reports indicating that patients with cancer generally experience higher levels of anxiety and reduced QoL.[41,43] Recent advances in systemic therapies have expanded treatment options and extended survival in patients with metastatic PPGLs. As a result, understanding their QoL has become increasingly important to guide supportive care in long-term patient management.[44,45] Reflecting this, the international consensus statement on diagnosis and management of PPGLs in children and adolescents has emphasized the need for psychological support for children and their relatives at diagnosis, during genetic counseling, and throughout follow-up.[46]

In our cohort, patients with unresected HNPGLs reported significantly lower physical QoL compared to the age-related general population. Previous studies also found a decreased QoL in patients with HNPGLs with increased fatigue, dysphonia, and impaired physical functioning, as key contributors to decrease QoL.[24,25] HNPGLs, in contrast to pheochromocytomas, are often non-secreting and symptoms are related to local mass effects instead of catecholamine secretion.[47] Cranial nerve involvement can lead to swallowing or speech difficulties and especially tympanic paragangliomas can cause pulsatile tinnitus or hearing loss. In another study, no differences in QoL in HNPGLs patients undergoing surgery compared to a watchful waiting approach were found.[48] Importantly, cranial nerve palsy may result not only from the tumor mass itself but also from surgical intervention. The association of QoL with specific symptoms associated with the HNPGL could not be evaluated in the current analysis due to incomplete data. A recent report from the HNPGL registry at the University Medical Center Utrecht revealed overall similar QoL between sporadic (8/16 patients with PPGLs present at diagnosis, 7/16 no PPGL present at time of psychosocial assessment) and hereditary HNPGLs (40/84 patients with a hereditary predisposition for PPGLs but no PPGL present at the time of assessment) and found no decreased QoL compared to the healthy Dutch population.[49]

In our cohort, clinically relevant anxiety was frequently reported by all subgroups except the patients with resected HNPGLs. Overall, anxiety appeared elevated relative to general population reference levels, whereas MCS SF-12 was not negatively affected.[38] In a Portuguese study of patients at risk for the development of a PPGL, genetic-testing-related distress and uncertainty were associated with higher levels of neuroticism.[50,51] Studies investigating QoL in MEN2 patients, who have elevated risk for PPGL related to their *RET* PV, revealed that psychological distress is likely chronic in patients with MEN2 and, in particular, the possibility of inheriting the disease to offspring resulted in an additional psychological burden.[52-54] In our cohort, patients who had resected PPGLs but no known PV also experienced elevated anxiety levels, comparable to those with germline PV.

Our findings of reduced self-reported physical health in PV carriers without a history of PPGL and in patients with active disease (metastatic PPGLs and unresected HNPGLs) highlight the need for structured psychosocial support beyond routine endocrine follow-up. Individuals who test positive for a susceptibility gene should be offered psychological counseling at the time of genetic diagnosis, with repeated offers during annual surveillance, ideally accompanied by brief mental-health screening.[46,55] The impaired QoL observed in patients with unresected HNPGLs also underlines the importance of systematic assessment of tumor-related symptoms such as dysphagia, dysphonia, tinnitus, or hearing loss. When present, early referral to otorhinolaryngology is indicated.[56,57]

A key strength of this study is the inclusion of patients with metastatic PPGLs, those with long-term follow-up after resection of a PPGL, and PV carriers without manifest disease, allowing assessment of the psychological burden across groups. Limitations include the challenge of assessing QoL before and after resection due to the urgency of surgery, making it difficult to isolate the impact of catecholamine excess. The small sample size limits analysis of QoL in carriers of high-risk mutations such as *SDHB*. Additionally, QoL assessments are inherently subjective and influenced by personal, cultural, and psychological factors. While primarily cross-sectional, the ongoing *ProsPheo* trial will enable future longitudinal analyses.

Conclusions

In summary, our study demonstrates significantly reduced self-reported physical health in susceptibility gene carriers without a history of a PPGL, patients with metastatic PPGLs, and those with unresected HNPGLs. In metastatic PPGLs, catecholamine excess was associated with reduced physical health, underscoring the need to prioritize symptom control in this subgroup. Physical health was impaired in PV carriers without history of a PPGL despite their younger age, indicating that the cumulative burden of comorbidities and psychosocial factors should not be underestimated. These findings support proactive assessment and targeted supportive interventions in this high-risk, predominantly young population. QoL in patients with resected, non-metastatic PPGLs was, independent of susceptibility gene carrier status, comparable to the general population. These findings underline that, aside from those with metastatic disease, most patients with a history of curative PPGL resection without residual disease maintain good physical and mental health, and routine follow-up does not appear to compromise QoL.

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Authors' contributions

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Conflict of interest

Co-author F.B. serves on the editorial board of the European Journal of Endocrinology. He was not involved in the review or editorial process for this paper, on which he is listed as an author. All other authors have nothing to disclose.

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Data availability

Restrictions apply to the availability of some or all data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

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