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Clinical Research Article

Recurrent Disease in Patients With Sporadic Pheochromocytoma and Paraganglioma

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- PPGLs exhibit a 15% to 20% prevalence of recurrence
- which may become apparent **decades** after primary tumor resection
- Recurrence PPGL mainly involves **metastatic** disease and associated with heightened morbidity and mortality
- There remain no histopathological methods to reliably assess potential recurrence after resection of the primary tumor
- Therefore, follow-up is recommended for all patients

- Close to 35% of patients with PPGL have hereditary disease
- Patients with PPGL due to pathogenic variants in **cluster 1 genes** that cause activation of **hypoxia** signaling pathways have high rates of **recurrent** disease . lifelong follow-up is recommended
- Recurrence rates are **significantly lower** in patients with PPGL due to pathogenic variants in **cluster 2 genes**, which are associated with activation of **kinase** signaling pathways
- Nevertheless, lifelong follow-up is still considered essential

- Although the need for follow-up is clearly established for patients with hereditary PPGL, the need for follow-up on patients with **sporadic** tumors remains unclear
- systematic reviewof 38 studies indicated a 5-year probability of recurrence among patients with sporadic PPGL of 4.7%
- in another systematic meta-analysis prevalence of recurrence among patients with sporadic pheochromocytoma did not exceed 3%
- again raising questions concerning need for follow-up

- heightened risk of recurrence:
- hereditary predisposition,
- younger age at initial tumor diagnosis
- extra-adrenal tumor location,
- larger tumor size
- higher levels of dopamine and its metabolite, methoxytyramine

- aim of this study was to investigate the **prevalence** of **recurrent** disease among patients with **sporadic** PPGL
- second objective was to identify **predictors of recurrence** that might be useful to triage any need for follow-up.
- we also **compared the prevalence** of recurrence in patients with sporadic PPGL with that in patients with hereditary disease due to pathogenic variants in cluster 1 and cluster 2 genes.

Methods
Study Design

- retrospective data from 1127 patients with PPGL enrolled at 1 quaternary center and 7 tertiary clinical centers

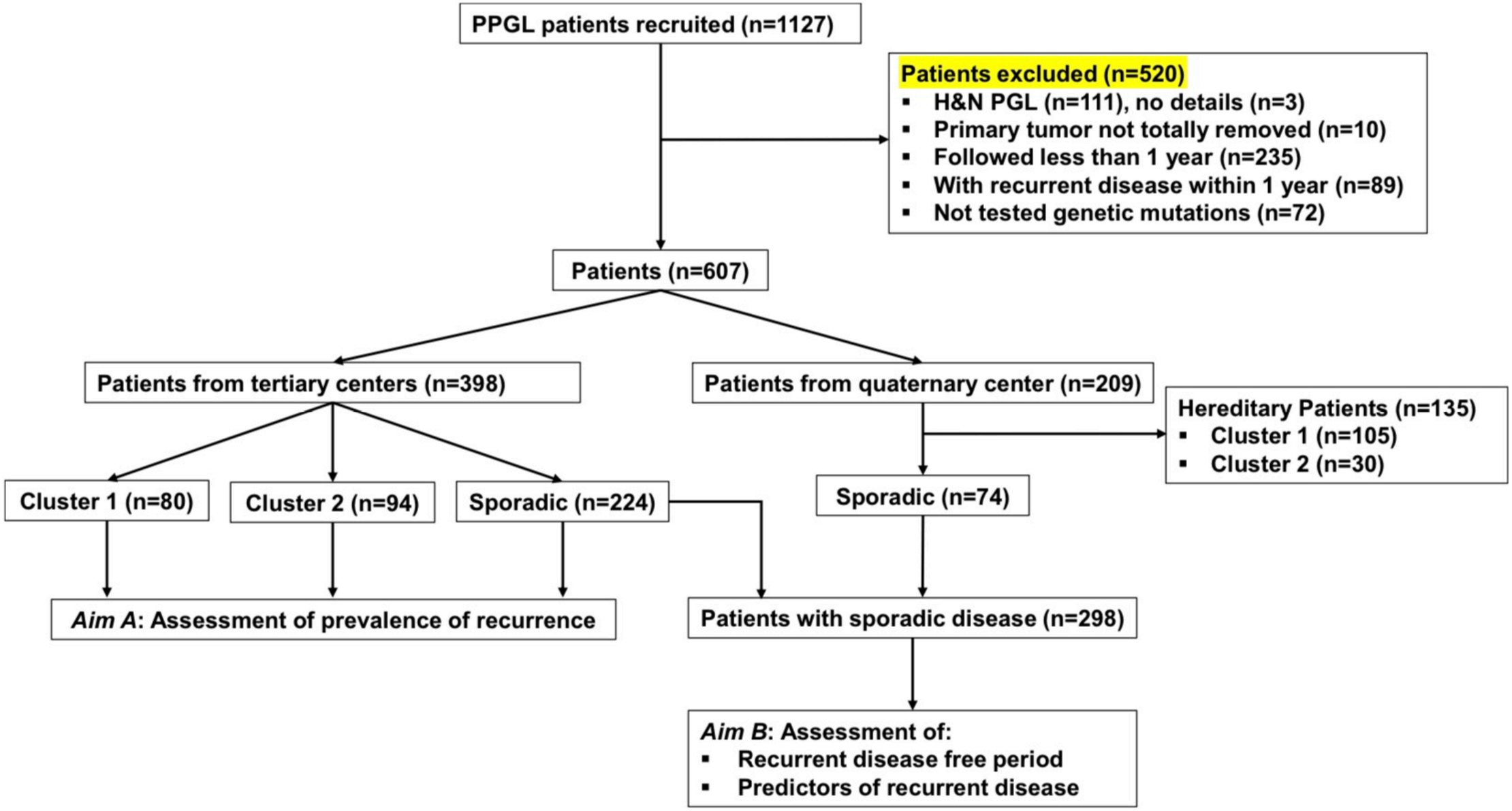

Figure 1. Flow chart of patients enrolled in the study.

Clinical Data Collection

- clinical information included sex and age at primary tumor diagnosis, locations and size of primary tumors, genetic test results, and tumor catecholamine biochemical phenotypes as assessed from measurements of **plasma free metanephrines ,free normetanephrine_and methoxytyramine.**
- Diagnosis of primary tumors was based on histopathological examination of surgically resected specimens.
- Patients with multifocal tumors located both within and outside of adrenal glands were classified as having extra-adrenal PPGL.

Clinical Data Collection

- **Recurrence** was defined as the presence of locoregional and/or a new PPGL and/or metastatic disease, at least 1 year after complete surgical resection of primary tumors.
- recurrence was diagnosed in **conventional and occasionally functional imaging studies after a positive biochemical test during follow-up.**
- **Confirmation** of recurrent disease required **histopathological** examination of surgically resected or biopsied tissue or diagnosis of inoperable metastases according to combinations of conventional and functional imaging studies.

Biochemical Measurements

- Measurements of **plasma free normetanephrine, metanephrine,and methoxytyramine** were performed using liquid chromatography with electrochemical detection or tandem mass spectrometry
- Designation of an **adrenergic biochemical phenotype** required an elevated plasma concentration of metanephrine above 62 pg/mL (0.31 nmol/L) and a tumor-derived increase of metanephrine of more than 5% of the combined increases of normetanephrine, metanephrine, and methoxytyramine .
- All other tumors with positive biochemical test results, including those with predominantly increased plasma methoxytyramine, were defined as **noradrenergic/ dopaminergic.**

Genetic Testing

- Genetic testing for **germline** pathogenic variants of SDHx,VHL, FH, MDH2, EPAS1, TMEM127, MAX, and RET was performed using next-generation sequencing and/or Sanger sequencing
- **somatic** pathogenic variants of VHL, RET, SDHB, SDHC, SDHD, MAX, and TMEM127, NF1,HRAS, and HIF2a genes.
- For **NF1**, the diagnosis was based mainly on genetic testing and on clinical manifestations according to established criteria

Genetic Testing

- **cluster 1 pathogenic variants : Germline** pathogenic variants in SDHA, SDHB, SDHC, SDHD, SDHAF2, VHL, FH, and MDH2, as well as mosaic variants of EPAS1 were classified
- **cluster 2 pathogenic variants: Germline** variants in TMEM127, MAX, RET, and NF1
- **sporadic disease: All other patients with negative germline genetic test results, with or without somatic pathogenic variants**

Statistical Analysis

Continuous data were expressed as medians and interquartile ranges (IQR). Mann–Whitney and Kruskal–Wallis tests were used for non-normally distributed continuous parameters.Chi-square or the Fisher exact test were used to compare categorical parameters. Bonferroni corrections were used for pairwise comparisons between subgroups. Cox proportional hazards regression models with hazard ratios (HR) were evaluated to study the association of clinical parameters with recurrent disease.

$P < 0.05$ was considered statistically significant.

Results
Clinical Characteristics

- Among 398 patients enrolled at the tertiary clinical centers,56.3% (224/398) had sporadic disease, 20.1% (80/398) had PPGL due to cluster 1 pathogenic variants, and 23.6% (94/398) PPGL due to cluster 2 pathogenic variants
- Patients with **sporadic** PPGL were **older** than those with hereditary tumors (P< 0.001)
- Patients with **sporadic** PPGL presented more often with **adrenal** tumors than those with PPGL due to cluster 1 pathogenic variants (94.2% vs 53.8%, P< 0.001), but not to those with tumors due to cluster 2 pathogenic variants (94.2% vs 98.9%).
- patients with **sporadic** PPGL presented more often (62.8% vs 2.9%, P< 0.001) with **adrenergic** tumors than those with cluster 1 pathogenic variants, but less often (62.8% vs 91.4% P < 0.001) than those with cluster 2 pathogenic variants.

Prevalence of Recurrent Disease Among Patients With PPGL

- Among patients with **sporadic** PPGL enrolled at the tertiary clinical centers, **14.7%** (33/224) were diagnosed with **recurrence**, predominantly due to **metastatic** (8%) disease (Table 1).
- Prevalence of recurrence among patients with **sporadic** PPGL was significantly **lower** (14.7% vs 47.5%, P< 0.001) compared to those with PPGL due to **cluster 1 pathogenic variants, but similar to those with cluster 2 pathogenic variant**s (14.7% vs 14.9%).
- This translated to a **2.45-fold higher risk of recurrence** in patients with PPGL due to **cluster 1** pathogenic variants compared to those with sporadic PPGL (P < 0.001), but similar risks of recurrence (P= 0.777) in patients with sporadic tumors and those with tumors due to cluster 2 pathogenic variants (Fig. 2A).
- The higher risk of recurrence was mainly related to **metastatic** disease, as patients with PPGL due to **cluster 1 pathogenic** variants presented with a **2.48-fold higher risk of metastasis** than those with **sporadic** PPGL (Fig. 2B).

Table 1. Clinical characteristics of patients enrolled at the tertiary clinical centers

	Cluster 1 PPGL	Cluster 2 PPGL	Sporadic PPGL
Number of patients	80	94	224
Age (years) at first diagnosis, median (IQR)	28.7 (20.5-43.8)	46.8 (31.9-59)[a]	52.9 (42.5-62.4)[a,b]
Males	47.5% (38/80)	41.5% (39/94)	44.6% (109/224)
Location			
Adrenal	53.8% (43/80)	98.9% (93/94)[a]	94.2% (211/224)[a]
Extra-adrenal	46.3% (37/80)	1.1% (1/94)[a]	5.8% (13/224)[a]
Biochemical phenotype			
Adrenergic	2.9% (2/68)	91.4% (74/81)[a]	62.8% (113/180)[a,b]
Noradrenergic/dopaminergic	97.1% (66/68)	8.6% (7/81)[a]	37.2% (67/180)[a,b]
Size of primary tumor (cm), medians (IQR)	3.6 (2.6-4.8)	3.5 (2.4-5.0)	4.1 (2.8-5.8)
With recurrent disease	47.5% (38/80)	14.9% (14/94)[a]	14.7% (33/224)[a]
Local recurrence/new tumor only	22.5% (18/80)	13.8% (13/94)	6.7% (15/224)[a]
With metastasis	25% (20/80)	1.1% (1/94)[a]	8% (18/224)[a,b]
Follow-up (years), median (IQR)	8.7 (5.2-16.3)	5.3 (3.1-9.8)[a]	7 (4.6-10)[a]

Abbreviations: IQR, interquartile range; PPGL, pheochromocytoma and paraganglioma.
[a]Significantly different from cluster 1.
[b]Significantly different from cluster 2.

- In order to avoid overestimation of recurrence due to referral bias, we then analyzed the prevalence of recurrence only among patients **without a previous history of PPGL and who had a follow-up period of at least 5 years.**

Table 2. Clinical characteristics of a subgroup of patients enrolled at the tertiary clinical centers, as defined by the following 2 criteria: absence of previous history of PPGL and a follow-up duration of more than 5 years

	Cluster 1 PPGL	Cluster 2 PPGL	Sporadic PPGL
Number of patients	26	27	96
Age (years) at first diagnosis, median (IQR)	27.2 (16.5-45.9)	48.8 (28.2-58.9)[a]	53.4 (44.3-62.7)[a]
Males	42.3% (11/26)	33.3% (9/27)	39.6% (38/96)
Location			
Adrenal	65.4% (17/26)	96.3% (26/27)[a]	95.8% (92/96)[a]
Extra-adrenal	34.6% (9/26)	3.7% (1/27)[a]	4.2% (4/96)[a]
Biochemical phenotype			
Adrenergic	0	88.9% (24/27)[a]	65.6% (63/96)[a]
Noradrenergic/dopaminergic	100% (26/26)	11.1% (3/27)[a]	34.4% (33/96)[a]
Size of primary tumor (cm), median (IQR)	3.7 (2.5-4.3)	3.6 (2-4.5)	4 (2.9-5.7)
With recurrent disease	23.1% (6/26)	11.1% (3/27)	6.3% (6/96)[a]
Local recurrence/new tumor only	11.5% (3/26)	11.1% (3/27)	5.2% (5/96)
With metastasis	11.5% (3/26)	0	1.0% (1/96)[a]
Follow-up (years), median (IQR)	8.2 (6.2-10.4)	8.2 (5.6-11.4)	7.3 (6.2-9.5)

Abbreviations: IQR, interquartile range; PPGL, pheochromocytoma and paraganglioma.
[a]Significantly different from cluster 1.

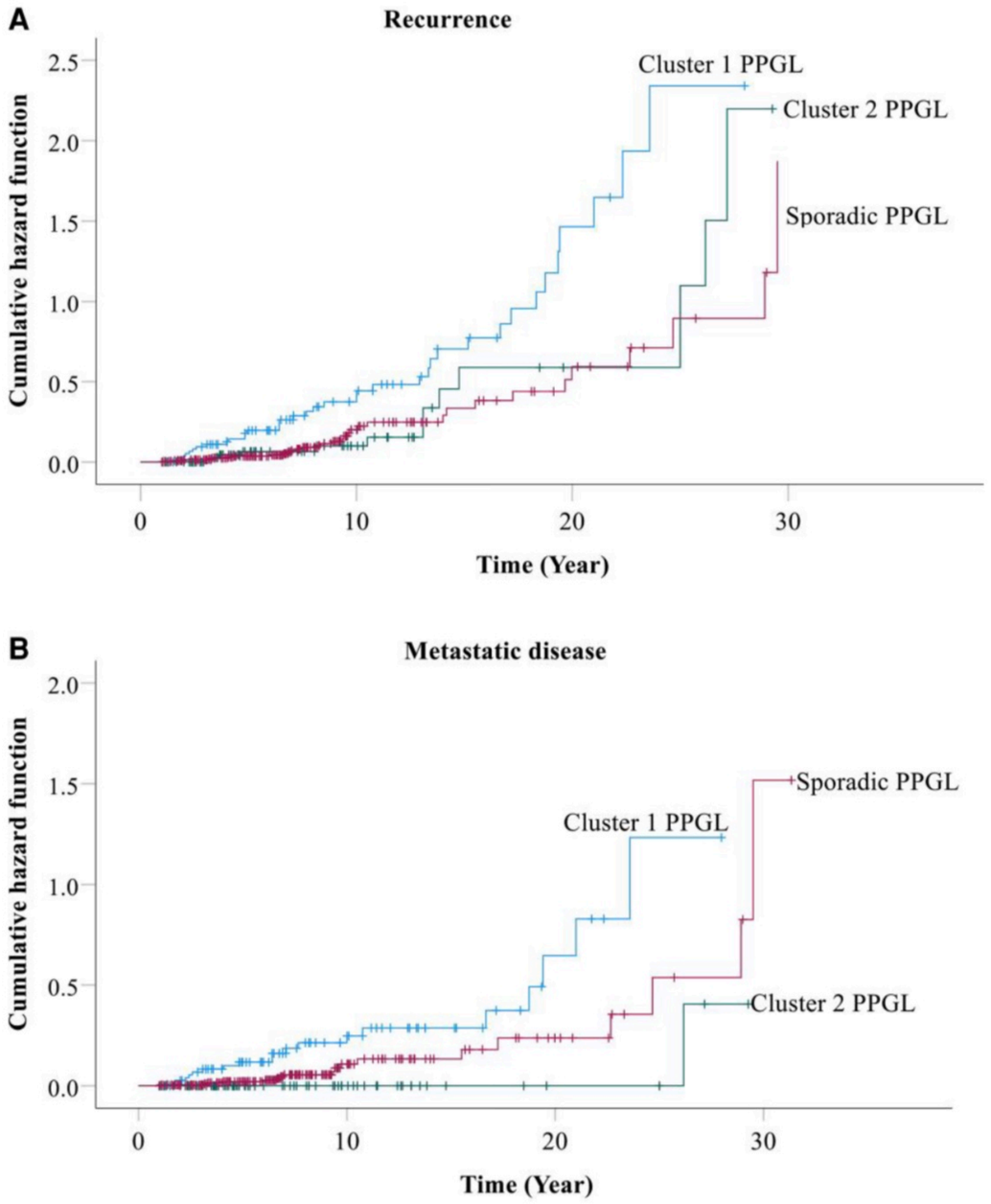

Figure 2. Cumulative hazard of recurrence (A) and only metastatic disease (B) among patients with sporadic vs hereditary PPGL. Patients with cluster 1 PPGL presented with a 2.45-fold higher risk of recurrence compared with those with sporadic tumors, whereas risk of recurrence was similar between patients with cluster 2 and sporadic PPGL (A). Similarly, patients with cluster 1 PPGL presented with a 2.48-fold higher risk of metastasis compared with those with sporadic tumors, whereas risk of recurrence was similar between patients with cluster 2 and sporadic PPGL (B).

Prevalence of Recurrent Disease Among Patients With **sporadic** PPGL

- After excluding 13 cases of patients with **sporadic paraganglioma**, prevalence of recurrence among patients with **sporadic pheochromocytoma** was only slightly reduced to 14.2%
- In **sporadic** PPGL, those with an **adrenergic** biochemical phenotype presented with **lower prevalence of recurrent disease** (9.7% vs 26.9%, P< 0.001) than those with a noradrenergic/dopaminergic biochemical phenotype.
- Importantly, the prevalence of recurrent disease was reduced to 3.2% for patients with **small (< 3 cm) sporadic adrenergic** PPGL.

Time to Detected Recurrence

- Among those 79 patients with **sporadic** recurrent PPGL, **only** 34.2% (27/79) were diagnosed with recurrence **within the first 5 years of diagnosis** of the primary tumor, whereas 29.1% and 17.7% were respectively diagnosed with recurrence **after 10 and 15 years of follow-up** (Fig. 3A).

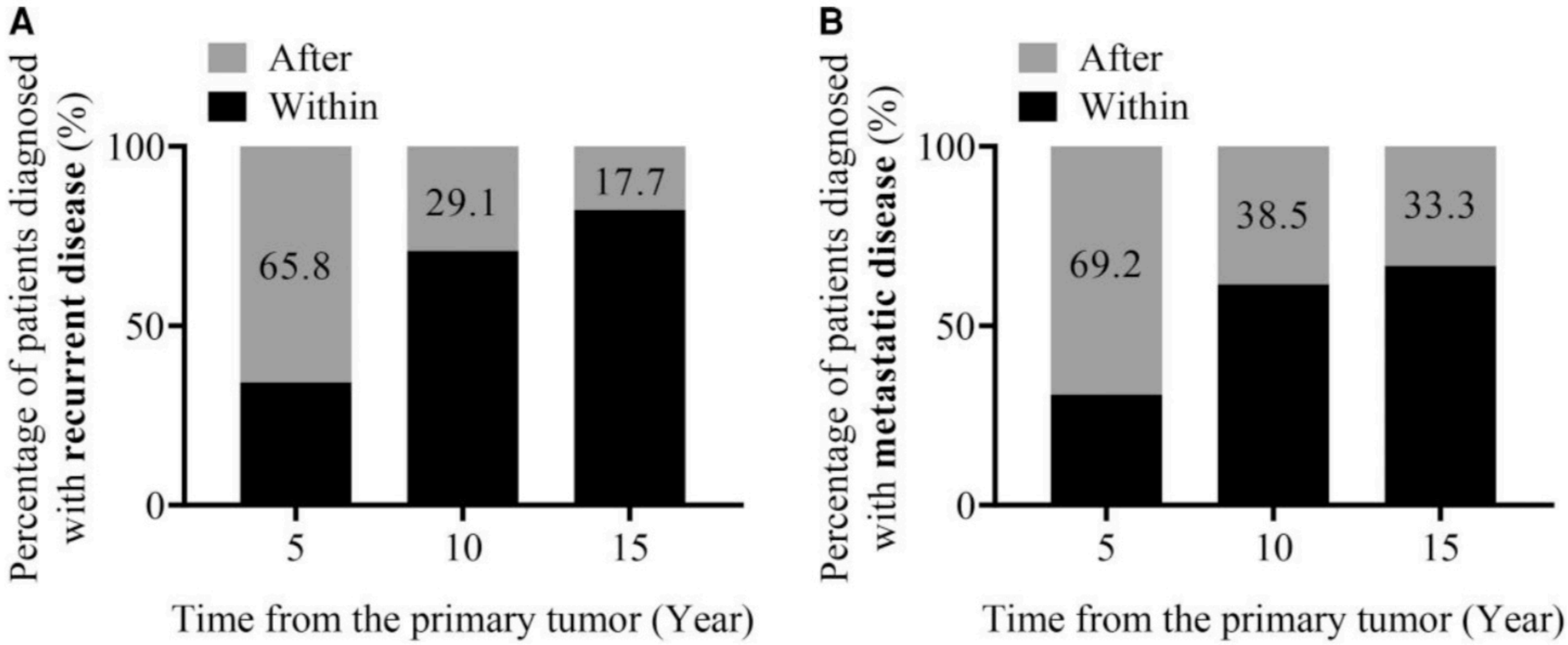

Figure 3. Recurrence- (A) and metastasis- (B) free period of patients with sporadic PPGL and recurrent disease. Percentage of patients that developed recurrence (A) or only metastatic disease (B) within the specific time periods (5, 10, 15 years) corresponds to the black part of each bar.

Time to Detected Recurrence

- Compared to those with noradrenergic/dopaminergic PPGL, patients with **adrenergic** tumors were diagnosed with recurrent disease at a **later** time point (P< 0.001)
- Similarly, for patients with PPGL **smaller than 5 cm,** the recurrence-free period was significantly **longer** than for those with tumors larger than 5 cm [P< 0.001,
- Finally, patients with **sporadic pheochromocytom**a were diagnosed with recurrences at **later** time points than those with **sporadic paraganglioma**[P= 0.022

Predictors of Recurrent Disease

- Multivariable analysis showed that a **noradrenergic**/ **dopaminergic** biochemical phenotype (HR 2.73; 95% CI, 1.553-4.802; P< 0.001), **larger tumor size (≥ 5 cm**) (HR 1.82; 95% CI, 1.113-2.962; P= 0.017) and **extra-adrenal tumor** location (HR 1.79; 95% CI, 1.002-3.187; P= 0.049) remained **independent predictors of recurrence for patients with sporadic PPGL**

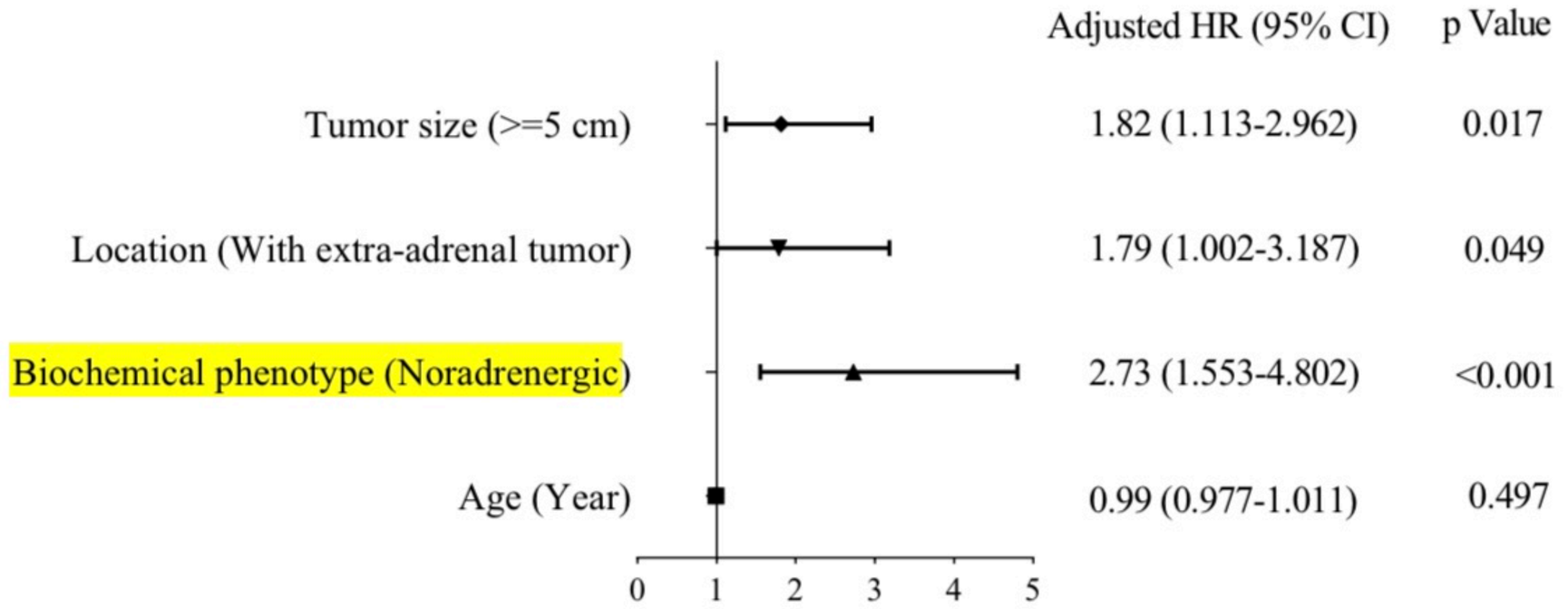

Figure 4. Multivariable Cox regression analysis for predictors of recurrent disease for patients with sporadic PPGL.

Discussion

- It is well established that patients with hereditary PPGL require long-term follow-up, whereas the need to follow patients with **sporadic** tumors remains **unclear**
- Our study is the first to focus on **sporadic** PPGL separately from hereditary tumors in one of the largest patient cohorts to date.
- Our findings of a **14.7% prevalence of recurrence** in patients with **sporadic** PPGL, including a significant proportion diagnosed **more than 10 years after** initial tumor diagnosis, indicate that **these patients also require long-term follow-up.**

Discussion

- The above conclusion and ***our results*** **contrast** with those of a recent systematic review by Holscher et al , where the prevalence of recurrent disease among patients with sporadic pheochromocytoma was calculated to be 3%, compared to 14.2% for sporadic pheochromocytoma in our study. This discrepancy can be largely explained by the shorter duration of follow-up in that meta-analysis,

Discussion

- patients with a previous history of sporadic PPGL included in our study may have led to overestimation of recurrence.
- In order to control for this confounder, we performed a subanalysis, excluding patients with previous history of PPGL.
- According to the above criteria, we found a 6.3% prevalence of recurrence among patients with sporadic PPGL
- Thus, we assume that the true prevalence of recurrence among patients with **sporadic PPGL is between 6.3% and 14.7%.** Prospective clinical trials are required to confirm this.

Discussion

- In our study, patients with PPGL due to **cluster 1** germline pathogenic variants presented with the **highest** rate of recurrence, mainly metastatic disease. This finding is **not surprising** and likely reflects different developmental origins of cluster 1 compared with cluster 2 or sporadic tumors.
- **prevalence of recurrent** disease among patients with **sporadic** disease was **similar** to that in patients with cluster **2** germline pathogenic variants. However, recurrent disease among patients with **sporadic** PPGL was **mainly** due to **metastases** (54.5%), whereas metastatic disease was rare among patients with tumors due to cluster 2 germline pathogenic variants (7.1%). **These findings support follow-up programs for patients with sporadic PPGL in addition to already established need in patients with cluster 1 germline pathogenic variants**.

Discussion

- 17.7% of patients with sporadic recurrent tumors were diagnosed with **recurrence** only **after 15 years** of follow-up, findings that might support **long-term follow-up beyond 15 years.**

Discussion

- **Despite** the implications of our study that patients with **sporadic** PPGL should receive **long-term follow-up**, the nature of **follow-up programs** could be tailored according to **specific patient characteristics.**
- In our study, larger tumor size and a noradrenergic/dopaminergic phenotype were associated with a higher risk of recurrence for patients with sporadic PPGL, **whereas those with small (< 3 cm) adrenergic tumors had a low (3.2%) prevalence of recurrence.** For the latter patients, the nature of follow-up may thus not be as exhaustive as for the former group.

Conclusion

- Patients with **sporadic** PPGL require **long-term follow-up** as they are at significant risk of recurrent disease, even 10 years after initial tumor diagnosis. Specific characteristics, such as **tumor size and biochemical tumor phenotype** could be used to guide individualized follow-up strategies for patients with sporadic PPGL.