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Pheochromocytoma and Paraganglioma in Children and Adolescents: Experience of the French Society of Pediatric Oncology (SFCE)

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Purpose: The purpose of this work is to assess the clinical outcome of pediatric patients diagnosed with pheochromocytoma and paraganglioma (PPGL) detected in France since 2000.

Methods: A retrospective multicenter study was conducted that included all patients younger than 18 years with PPGL diagnosed in France between 2000 and 2016. Patients were identified from 4 different sources: the National Registry of Childhood Solid Tumors, the French Pediatric Rare Tumors Database, the French registry of succinate dehydrogenase (SDH)-related hereditary paraganglioma, and the nationwide TenGen network.

Abbreviations: EFS, event-free survival; OS, overall survival; PGL, paraganglioma, PHEO, pheochromocytoma; PPGL, pheochromocytoma and paraganglioma; RNTSE, National Registry of Childhood Solid Tumors; SFCE, French Society of Pediatric Oncology.

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Results: Among 113 eligible patients, 81 children with available data were enrolled (41 with adrenal and 40 with extra-adrenal PPGL). At diagnosis, 11 had synchronous metastases. After a median follow-up of 53 months, 27 patients experienced a new event (n = 7 second PPGL, n = 1 second paraganglioma [PGL], n = 8 local recurrences, n = 10 metastatic relapses, n = 1 new tumor) and 2 patients died of their disease. The 3- and 10-year event-free survival rates were 80% (71%-90%) and 39% (20%-57%), respectively, whereas the overall survival rate was 97% (93%-100%) at 3 and 10 years. A germline mutation in one PPGL-susceptibility gene was identified in 53 of the 68 (77%) patients who underwent genetic testing (*SDHB* [n = 25], *VHL* [n = 21], *RET* [n = 2], *HIF2A* [n = 2], *SDHC* [n = 1], *SDHD* [n = 1], *NF1* [n = 1]). Incomplete resection and synchronous metastases were associated with higher risk of events ($P = .011$, $P = .004$), but presence of a germline mutation was not ($P = .11$).

Conclusions: Most pediatric PPGLs are associated with germline mutations and require specific follow-up because of the high risk of tumor recurrence.

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Key Words: pheochromocytoma, paraganglioma, pediatric, genetic, *SDHB*

Pheochromocytoma and paraganglioma (PPGL) are rare neuroendocrine tumors derived from chromaffin cells of the adrenal medulla for pheochromocytoma (PHEO) or of extra-adrenal paraganglia for paraganglioma (PGL). Only 10% to 20% of tumors are detected before age 18 years, with an incidence of 0.2 to 0.5 cases per million [1, 2].

Unlike other malignant diseases, up to recently no specific histological or molecular markers existed to evaluate PPGL malignancy at first surgery [3]. The revised World Health Organization recommendations have defined malignant PPGL as metastatic disease that is histologically diagnosed by the presence of chromaffin tissues in organs that usually lack chromaffin cells [4]. Metastases mostly occur in lymph nodes, bones, lungs, and the liver. PPGLs are considered neuroendocrine tumors with the highest frequency of genetically determined cases. In pediatric patients, 50% to 70% of PPGLs are driven by a germline mutation in a PPGL-susceptibility gene [5]. Many PPGL-susceptibility genes have been identified and their list grows every year. Transcriptomic studies, using different large cohorts, have shown that genetically determined PPGLs are separated into 2 clusters. Tumors in cluster 1 carry mutations in the *VHL*, *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *FH*, *MDH2*, *GOT2*, *SLC25A11* or *HIF2A* gene, and are characterized by induction of a pseudo-hypoxic tumorigenic pathway. Tumors in cluster 2 harbor mutations in the *RET*, *NF1*, *TMEM127* or *MAX* gene, and are characterized by activation of the mitogen-activated protein kinase and mTOR signaling pathways [6, 7]. The clinical outcome of patients with sporadic PPGL seems more favorable than that of patients with genetic forms, which are characterized by an early onset and high risk of multiple PPGLs or other syndromic lesions. It has been reported that the incidence of metastases is higher in PPGLs with an *SDHB*, *SLC25A11*, and *FH* mutation than in sporadic PPGLs, or PPGLs associated with other germline mutations [6, 7, 8]. The objective of this study was to determine the clinical outcome of children and adolescents with PPGL diagnosed in France between 2000 and 2016.

1. Methods

A. Patients

All patients with a PPGL diagnosed in France between 2000 and 2016 before age 18 years were eligible. Pediatric patients were identified in the National Registry of Childhood Solid Tumors (RNTSE). In addition, all centers of the French Society of Pediatric Oncology

(SFCE), the French registry of SDH-related hereditary paraganglioma (PGL.R), the TenGen network, and the French Rare Pediatric Tumor database (FRACTURE) [9], as well as all pediatric pathology and surgery units in Paris, were contacted to identify additional cases. There were no specific guidelines in France for treatment and follow-up of pediatric PPGL.

B. Clinical Information

A case report form was used to collect demographic, clinical, and biochemical data as well as the tumor histological characteristics, detailed description of the clinical management, and outcome. The family clinical history and the genetic analysis results, when PPGL genetic testing was performed, were also recorded. In accordance with French law, the parents of each child signed an informed consent before genetic testing. Measurements of tumor largest diameter were based on computed tomography imaging. The French FRACTURE database has obtained legal and ethical approval from the French Data Protection Authority (CNIL) registration number DR-2011-408, and date October 14, 2011.

C. Statistical Analyses

Statistical analyses were carried out using GraphPad Prism software. Results were reported as medians with ranges for quantitative data, and as numbers and percentages for qualitative data. Overall survival (OS) was defined as the time from diagnosis to death or last follow-up. Event-free survival (EFS) was defined as the time from diagnosis to disease progression, second malignancy, death whatever the cause, or last follow-up. Several prognostic factors (tumor type [PHEO or PGL], tumor size ≥ 5 cm or < 5 cm], quality of surgical resection [complete or incomplete], presence of metastases at diagnosis or not, and identification of a mutation in a PPGL-susceptibility gene vs no germline mutation identified) were evaluated using Peto's test rather than unweighted log-rank tests because the relatively short follow-up time required a specific analysis of late events with very few patients at risk. All tests were 2-sided with a confidence level of 5%.

2. Results

A. Demographic and Tumor Characteristics

Overall, 77 patients with a PPGL that was diagnosed between 2000 and 2016 were registered in the RNTSE and treated in the 18 SFCE centers participating in this study. In addition, 36 patients with PPGL who were not registered in the RNTSE were identified in the archives of the participating SFCE centers for the 2000 to 2016 period. Among these 113 patients, 81 had available clinical data and were included in the analysis.

The tumor characteristics are detailed in [Table 1](#). The tumor site was adrenal in 41 patients and extra-adrenal in 40. The median age at diagnosis was 13.3 years (range, 2.2-18 years). In 75 patients (93%), clinical symptoms, such as abdominal pain or high blood pressure, led to the diagnosis. The tumor was detected during a systematic clinical screening in 6 patients identified as mutation carriers in families with PPGL predisposition. Five patients (6%) had a previous or a synchronous malignancy: medullary thyroid carcinoma (n = 1 patient with multiple endocrine neoplasia type 2), Wilms tumor (n = 1 patient with Beckwith-Wiedemann syndrome), ependymoma (n = 1), Poppema nodular paraganglioma (n = 1), and gastrointestinal stromal tumor associated with PGL and pulmonary chondroma, as part of the Carney triad (n = 1).

At diagnosis, PHEO (total n = 41) were unilateral in 37 (90%) patients, and bilateral in 4 patients. Among the 40 PGLs, 33 were unique and 7 (17%) multiple, and 25 (62%) were located in the abdomen. In 11 patients, PPGL was metastatic at diagnosis with histologically proven synchronous lymph node metastases (n = 7), and/or a metastatic spreading in bones (n = 3) and lungs (n = 3) (multiple sites possible).

Table 1. Clinical, biochemical, and treatment characteristics of patients with pheochromocytoma and paraganglioma: baseline data

	Pheochromocytoma		Paraganglioma
No. of patients	41 (50%)		40 (50%)
		Abdomen	25 (62%)
		Pelvis	1
		Thorax	5 (12.5%)
		Neck	7 (17.5%)
		Head	2 (5%)
Unilateral	37 (91%)		
Bilateral	4 (9%)		
Sex: male	28 (68%)		20 (50%)
Age at diagnosis (median, range), y	11.5 (2.2-18)		13.3 (4, 6-18)
Detected by clinical screening after positive presymptomatic genetic test (number, percentage)	5 (12%)		1 (2.5%)
Synchronous metastases	5 (12%)		6 (15%)
Tumor largest diameter			
< 5 cm	20 (50%)		22 (61%)
5-10 cm	20 (50%)		11 (30.5%)
> 10 cm	0		3 (8.3%)
Missing data	1		4
Fractionated metanephrines/urinary creatinine			
> 3 N	31 (86%)		25 (69%)
N	5 (13.8%)		11 (30.5%)
Not available	5		4
Treatment			
Primary resection	40 (97%)		38 (74%)
Complete excision	33 (82%)		28 (73%)
Microscopically incomplete	5 (12.5%)		7 (18.4%)

Measurements of tumor largest diameter were based on computed tomography imaging.

Abbreviation: N, laboratory normal values.

B. Treatment Characteristics and Clinical Outcome

Up-front tumor resection was performed in 78 (96%) patients. Primary tumor resection was complete in 61 patients, microscopically incomplete in 12, and macroscopically incomplete in 5. Seven patients received additional therapies: chemotherapy (n = 4), external radiotherapy on the tumor bed (n = 4), and metabolic radiotherapy with ¹³¹I-mIBG (¹³¹I-metaiodobenzylguanidine) (n = 1).

The median follow-up was 53 months (range, 2-173 months). Six patients were lost to follow-up 1 to 9 months after surgery. During this period, 27 patients (n = 14/41 with PHEO and 13/40 with PGL) experienced an event. The median time between the initial diagnosis and the first event was 48 months (range, 1-133.2 months), but late events after 5 years were reported in 8 of 30 patients (n = 4 with PHEO and n = 4 with PGL). Specifically, one patient with von Hippel Lindau disease had a non-PPGL second malignancy (clear cell carcinoma) 38 months after the initial PHEO diagnosis. A new PPGL was detected for 8 patients, among whom 7 patients had a new PHEO in the contralateral adrenal gland after a median follow-up of 45.6 months (range, 1-82.1 months), and 1 patient had multiple new cervical PGLs. Local relapse occurred in 8 patients (n = 2 with PHEO and n = 6 with PGL), after a median time of 38.5 months (range, 3-134 months). Primary tumor resection was complete in 4 patients, incomplete in 3 patients, and 1 could not undergo surgery but received external radiotherapy on the tumor bed. Metastatic relapse was recorded for 10 patients (n = 4 with PHEO and n = 6 with PGL), within a median time of 44.5 months (range, 1-96 months]. The 3-year and 5-year EFS rates were 55% (23%-78%) and 33% (9%-61%) respectively in patients with metastatic disease.

Among the 27 patients with an event after the first PPGL diagnosis, 9 (33%) had multiple metastatic relapses leading to the death of 2 patients, 9 and 10 months after the initial diagnosis. No other death was reported among the patients included in this series.

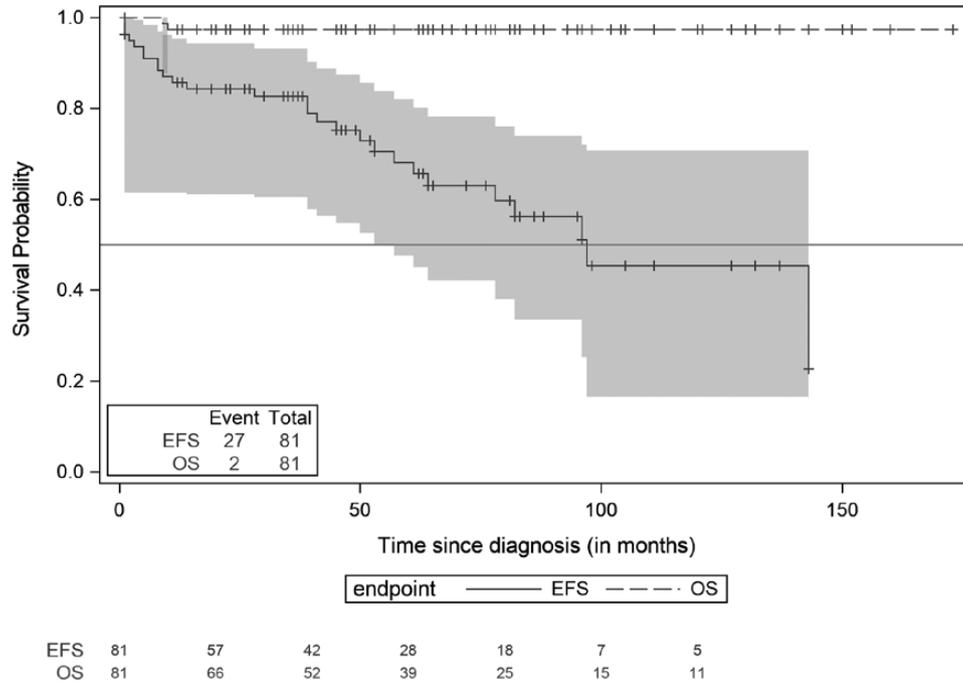


Figure 1. Event-free survival and overall survival of patients with pheochromocytoma and paraganglioma (95% CI). Kaplan-Meier survival curves and 95% confidence band: overall survival (OS) and event-free survival (EFS) curves of pediatric patients diagnosed with pheochromocytoma and paraganglioma. Two patients died, and 27 presented with a new event.

Overall, the 3-year, 5-year, and 10-year EFS rates were 80% (71%-90%), 61% (47%-75%), and 39% (20%-57%), respectively, and the OS rate was 97% (93%-100%) at 3, 5, and 10 years after diagnosis (Fig. 1). In this cohort, incomplete surgical resection of the initial PPGL and presence of a metastatic disease at the initial diagnosis were associated with a significant higher risk of local and metastatic relapses ($P = .011$, and $P = .004$), respectively (Figs. 2 and 3).

C. Genetic Testing

A pathogenic germline mutation in a PPGL-susceptibility gene (*SDHB* [$n = 25$], *VHL* [$n = 21$], *RET* [$n = 2$], *HIF2A* [$n = 2$], *SDHC* [$n = 1$], *SDHD* [$n = 1$], and *NF1* [$n = 1$]) was identified in 53 out of the 68 (77%) patients who underwent genetic testing (Table 2). The genotype-phenotype correlations are reported in Table 2. The mutation rate was 77% in patients with PHEO (27/35) and 78% in patients with PGL (26/33). Among the patients with genetic testing results, 24 were in the group of 27 patients who had an event during follow-up, and 22/24 (92%) carried a mutation: *SDHB* ($n = 9$), *VHL* ($n = 9$), *SDHC* ($n = 1$), *RET* ($n = 1$), *HIF2A* ($n = 1$) and *NF1* ($n = 1$). Among the 68 children who underwent genetic testing, neither the identification of a germline mutation ($P = .11$) nor the *SDHB* mutation status ($P = .83$) had a significant impact on outcome.

3. Discussion

Over the last decade, many reports have described PPGL clinical and genetic characteristics in large series of adult patients. These insights have helped to reduce treatment-related morbidity and mortality, with efficient and gene-specific preventive strategies. However, the subgroup of pediatric PPGL is still poorly studied because previous reports were mostly based on

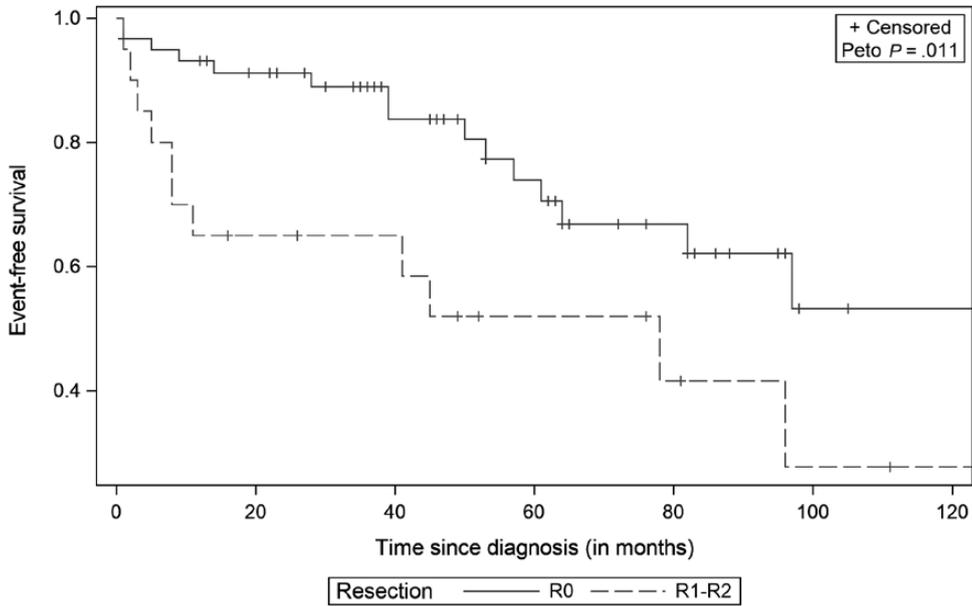


Figure 2. Event-free survival of patients with complete resection (R0) and with incomplete resection (R1-R2) (95% CI). Comparison of event-free survival (EFS) between patients with primary complete tumor resection (N = 61), and patients with incomplete tumor resection (N = 20). Incomplete resection was associated with a higher risk of events ($P = .011$).

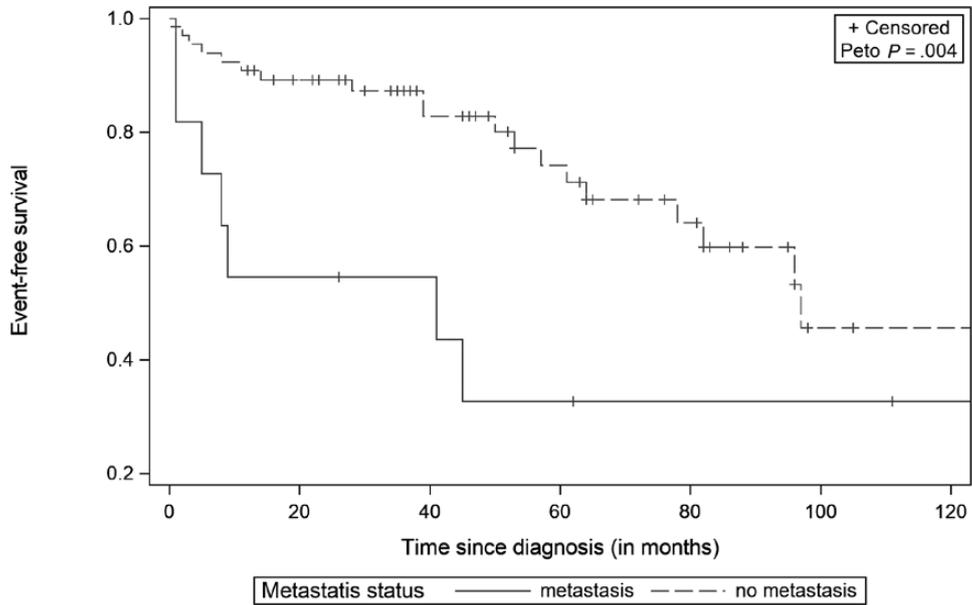


Figure 3. Event-free survival of patients with and without metastases (95% CI). Comparison of event-free survival (EFS) between patients without metastasis disease at diagnosis (N = 70), and patients with metastasis disease at diagnosis (N = 11). Presence of synchronous metastases at diagnosis was associated with a higher risk of events ($P = .004$).

Table 2. Clinical characteristics and relationship with local and distant metastases

Mutated gene	<i>SDHB</i>	<i>VHL</i>	<i>SDHC</i>	<i>SDHD</i>	<i>HIF2A</i>	<i>NF1</i>	<i>RET</i>
No. of patients	25	21	1	1	2	1	2
Median age (range), y	13.3 (6.6-18)	11 (2-18)	16	11	10.1 (9.1-10.3)	12	17 (14.6-18)
Sex: male	13	14	0	0	1	1	2
PHEO	7	17	0	0	1	0	2
PGL	18	4	1	1	1	1	0
Metastasis at diagnosis	1	2	1	0	1	1	0
Event	9	9	1	0	1	1	1
PHEO	1	9	0		1	0	1
PGL	8	0	1		0	1	0
Median time to event, mo	45	39	45	0	8	20	72
Second non-PPGL tumor		1					
Metachronous PPGL	–	7	1		–	–	–
Local relapse	7	–	–		–	–	1
Metastatic relapse	2	1	0		1	1	–

Abbreviations: PHEO, pheochromocytoma; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma.

few cases [2, 10, 11-16]. The present study described 81 patients with PPGL diagnosed before age 18 years, one of the largest series of pediatric patients [15, 6, 17-22] (Table 3).

The patients' recruitment from the RNTSE supports the representativeness of this cohort. Although patients with tumors classified as benign are not systematically included in the registry, patients who were identified in the archives of the pathology and surgery departments in Paris were also addressed at SFCE centers. In our cohort, despite a relatively short follow-up time, 27 (33%) patients presented with an event: Twenty-six patients had tumor relapses, including 10 (38%) metastatic relapses and 1 patient with a non-PPGL second malignancy. In addition, among the 68 (83%) patients who underwent genetic testing for mutations in PPGL-susceptibility genes, 53 (77%) had a pathogenic mutation, including 25 (47% of mutation carriers) with an *SDHB* mutation. These mutation rates are in line with previous reports (see Table 3).

Five patients (6%) had a previous malignancy. Tumors of the multiple endocrine neoplasia type 2, von Hippel Lindau disease, and neurofibromatosis type 1 spectra can be associated with PPGL [7, 23-26]. Conversely, PPGL association with nephroblastoma and ependymoma is rare. However, few cases of PHEO in patients with Beckwith-Wiedemann syndrome have been described [27], and a recent genetic analysis reported a D631Y *RET* mutation in a patient with recurrent anaplastic ependymoma associated with a familial history of PHEO [28]. In our cohort, the patient with PHEO after an ependymoma (n = 1) did not undergo genetic testing, but the clinical and familial features did not suggest a multiple endocrine neoplasia type 2.

The proportion of patients with metastatic PPGL at diagnosis was high: Fourteen percent of patients had synchronous metastases, and 38% of patients who relapsed had metachronous metastases, including 4 patients with localized PPGL at diagnosis. In our analysis, the presence of metastases at diagnosis was associated with a higher risk of recurrence and a 5-year EFS rate of 33%. Our results are in line with previous reports, in which the 5-year survival rate of pediatric patients with nonmetastatic PPGL was 90% [29] and ranged from 30% to 60% in patients with metastatic disease for whom the 10-year survival rate was 31% [30-32]. The prognostic impact of incomplete surgical resection has to be stressed. In our study, incomplete resection at first surgery was significantly associated with a higher risk of an event. Indeed, surgery is the only curative option for localized PPGL. In our study, the 10-year OS rate was 97%, despite the high rate of events during the follow-up (27/81, mostly tumor recurrences). However, we must acknowledge that late events may have been underestimated in our series because the median follow-up was rather short. Indeed, in our series, 27% of patients with more than 5 years of follow-up experienced a late

Table 3: Review of literature data

Authors and date of publication	Patients, No.	Age at diagnosis, y	PHEO/PGL ratio	PGL localization: abdomen, thorax, neck, other	PHEO: bilateral at diagnosis, No.	New PPGL, No., %	Relapse (N) and %	Time to relapse	Metastatic at diagnosis No., %	Death No.	Percentage of mutation carriers in tested patients, %	Mutated gene: cluster 1 (SDHB, SDHC, SDHC, VHL) cluster 2 (RET, NFI, HIF2A)
Argentina, Barontini et al, 2006 [1]	58	11.0	4.2	7/1/-/1	5	16	7 (12%)	12-60 mo	0	4	39	Cluster 1 VHL 16; SDHB 1 Cluster 2 NFI 1; RET 2
USA, Pham et al, 2006 [22]	30	14.7	0.66	14/1/3/-	0	0	9 (30%)	0-103 mo	14 (46%)	0	100	Cluster 1 SDHB and SDHD 2 Cluster 2 RET 3
USA, King et al, 2011 [23]	49	11.6	0.26	22/-/3/-	0	0	32 (65%)	0-29 y	0	5	82	Cluster 1 VHL 6; SDHB 27; SDHD 4 Cluster 2 NFI 2
Multinational, Bausch et al, 2013 [5]	177	13	15.6	36/9/8/-	43	49	68 (38%)	0-25 y	10 (5%)	8	80	Cluster 1 VHL 80; SDHB 25; SDHD 17; SDHA 1 SDHC 1 Cluster 2 NFI 6; RET 1
Spanish, Cascon et al, 2013 [19]	36	13.8	0.62	17/5	7	-	-	-	4 (11%)	1	69	Cluster 1 VHL 8; SDHB 11; SDHD 4 Cluster 2 RET 1; MAX 1
India, Mishra et al, 2014 [20]	24	14-16	3	-	10	2	-	-	2 (8%)	3	0	Cluster 1 VHL 25; SDHB 36; SDHD 9 Cluster 2 NFI 1; RET 3
Multinational, Pamporaki et al, 2017 [18]	95	13.3	0.54	-	11	20	57 (60%)	6 mo-16 y	31 (32%)	-	80.4	Cluster 1 VHL 21; SDHB 13; SDHD 4; SDHA 1 Cluster 2 NFI 1; RET 3; MAX 1
USA, Babic et al, 2017 [21]	55	13.4	1.75	12/2/6/-	8	11	22 (40%)	6 mo-16 y	9 (16%)	-	80	Cluster 1 VHL 21; SDHB 25; SDHC 1; SDHD 1; HIF2A 2 Cluster 2 NFI 1; RET 3; MAX 1
Current study, 2019	81	13.3	1.02	25/5/7/3	7	7	27 (33%)	1-133.2 mo	11 (13.5%)	2	77	Cluster 1 VHL 21; SDHB 25; SDHC 1; SDHD 1; HIF2A 2 Cluster 2 NFI 2; RET 2
Total	605	13.2	3.07	133/23/27/4	91	105	222 (36%)	1 mo-29 y	81 (13.3%)	23	67.4	Cluster 1 VHL 177; SDHB 138; SDHC 2; SDHD 40; SDHA 2; HIF2A 2 Cluster 2 NFI 12; RET 13; MAX 2

Abbreviations: PHEO, pheochromocytoma; PGL, paraganglioma; PPGL, pheochromocytoma and paraganglioma; USA, United States of America.

relapse. This high incidence of late relapses in pediatric PPGL has already been reported in adult patients with PPGL diagnosed before age 20 years in whom the median interval between diagnosis and the first event was 9.1 years [23].

Since 2000, many PPGL predisposition genes have been identified [13, 25, 26, 33-36]. Recent studies showed that 50% to 70% of pediatric patients with PPGL carry a causal mutation [20, 29] (see Table 3). Indeed, mutations in *SDHB*, *SDHC*, *SDHD*, *VHL*, *RET*, and *NF1* are frequently associated with PPGL [18, 23, 25, 26, 35], whereas mutations in *SDHA*, *SDHAF2*, *TMEM127*, *HIF2A*, *FH*, *SLC25A11*, and *MAX* have been described only in limited series of patients [33, 34, 36, 37, 38]. Because this retrospective study covers a long period, genetic screening was not proposed as a systematic procedure for all patients, especially those with a PPGL diagnosed more than 10 years ago. Before 2006, only patients whose phenotype or family history suggested a predisposition syndrome were advised to undergo genetic counseling. In our cohort, among the 68 patients who underwent genetic testing, 53 (77%) were carriers of a pathogenic mutation in a PPGL-susceptibility gene. This proportion is probably underestimated because a large proportion of patients in whom no germline mutation was identified was tested by Sanger targeted sequencing before 2010, at a period when only a subset of the genes now known to be associated with a predisposition to PPGL were routinely analyzed. Therefore, a new analysis by next-generation sequencing with a panel including all identified PPGL-susceptibility genes might also identify a pathogenic mutation in patients with negative genetic testing results at the time of the diagnosis. This may increase the mutation detection rate in our cohort [39]. Nowadays, genetic counseling is recommended for all patients with PPGL [3, 29] to identify genetically determined PPGL and to propose predictive genetic testing to mutations carriers' relatives. The proportion of patients with an *SDHB* mutation was as expected in our series, but only one patient carried an *SDHD* mutation, which is rather low because this mutation is described in 7% to 11% of previous pediatric series of PPGL [5, 18, 19, 21, 22, 23]. This may be due to a bias in patient recruitment and may be because *SDHD* mutations are mostly associated with cervical PGL treated in ears, nose, and throat departments and less likely to be declared in the RNTSE, nor referred to pediatric oncology departments.

Among the 24 of 27 patients who presented with an event during the follow-up and underwent genetic testing, 22 (92%) carried a pathogenic genetic mutation in a PPGL-susceptibility gene. In our series, carrying a mutation in one of these genes was not shown to be associated with a significant increased risk of recurrence, despite a trend to higher risk of relapse after 40 months of follow-up. This result may be explained by the relatively short follow-up of *SDHB*-mutations carriers leading to a poor estimation of the risk of late event. Considering the high incidence of germline mutations in this population, careful and lifelong follow-up aiming at earlier detection and treatment of novel lesions is now recommended for all pediatric patients with PPGL.

In this study spanning more than 2 decades, the lack of guidelines for treatment and follow-up of pediatric PPGL led to suboptimal care because 7% of patients were lost to follow-up after surgery, 16% did not benefit from genetic testing, and most patients with negative genetic testing did not benefit from a new next-generation sequencing analysis of all PPGL-susceptibility genes. These results stress the need for guidelines for pediatric PPGL patients. In a large study comparing pediatric vs adult patients with PPGL, Pamporaki et al showed that despite the higher prevalence of metastatic disease in children, metastatic recurrences were mostly diagnosed in patients with PPGL during adulthood [18]. No evidence suggests that surveillance should be different in children compared with adults; however, pediatric oncologists should be aware of the importance of prolonging the follow-up of children with PPGL into adulthood. Considering the high risk of genetic predisposition in pediatric patients with PPGL, the current protocols recommend surveillance through regular examinations for early detection of recurrence or of new tumors for all pediatric patients with PPGL, as is done for high-risk adult patients (ie, patients with genetically determined disease, tumors greater than 50 mm, and extra-adrenal location) for whom lifetime follow-up is indicated [29]. The European practice guidelines for long-time follow-up recommend monitoring blood pressure and 24-hour urinary fractionated metanephrines and optionally chromogranin A

once a year, together with whole-body magnetic resonance imaging every 1 to 2 years, for the early detection of recurrence or of new tumors, while minimizing radiation exposure [29, 40, 41]. Neck magnetic resonance angiography may be discussed with specialists because PPGL detection may be difficult in the neck [40], regardless of genetic background.

4. Conclusions

This retrospective analysis underlines the need for improvement of pediatric care for patients with PPGL after surgery. Because of the high incidence of hereditary PPGL, genetic counseling and screening for germline mutations are mandatory to improve clinical follow-up guided by genetic background and for the detection of asymptomatic mutation carriers among relatives. Moreover, as suggested in international guidelines, all pediatric PPGL patients, regardless of the identification of a germline mutation, require careful and lifelong follow-up because of the high risk of late events.

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