Pheochromocytomas and paragangliomas in children: Data from the Italian Cooperative Study (TREP)

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Part of these data have been discussed as an oral presentation at the 48th Annual Congress of the International Society of Pediatric Oncology (SIOP) held in Dublin (Ireland) in 2016 (Pheochromocytomas and Paragangliomas in Children: Data from the Italian Multicenter Study (TREP project) on Rare Tumors in Childhood (2000-2014), Pediatric Blood & Cancer 63, S46-S46).

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Abstract

Background: Pheochromocytomas (PCs) are neuroendocrine tumors arising from the chromaffin cells of the adrenal gland, and paragangliomas (PGLs) are their extra-adrenal counterparts arising from ganglia along the sympathetic/parasympathetic chain. Surgery is the cornerstone of treatment. A sporadic or inherited germline mutation is commonly associated.

Materials and methods: Among over 1000 patients registered into the Tumori Rari in Età Pediatrica—rare tumors in pediatric age project—from 2000 to 2019, 50 were affected by PC/PGL. All clinical and therapeutic data were evaluated.

Results: Twenty-eight patients had PC and 22 had PGL. Age at diagnosis ranged between 5 and 17 years. Thirty-five patients had symptoms related to catecholamine hypersecretion; in 7 of 50 patients, diagnosis was incidental or done during assessment of a familial syndrome. In all cases, conventional imaging was effective to assess the presence of a tumor. In addition, 18 of 38 functional imaging studies were positive (61%). Forty-eight patients were eligible for surgery: a complete resection was more frequently achieved in PC than in PGL (26/28 vs 11/22). All relapses were treated with surgery alone, surgery plus medical treatment, or chemotherapy alone; one PC with metastasis at diagnosis received radiotherapy only. Forty-four patients were in the first, second, or third complete remission (10/50 recurred; 8/10 carried a germline mutation). Five of 50 patients were alive with disease. One patient died of disease.

Abbreviations: 18F-DOPA, fluorine-18-L-dihydroxyphenylalanine; 18F-FDG, fluorine-18-fluorodeoxyglucose; 123I-MIBG, 123iodine-metaiodobenzylguanidine; 177Lu-DOTATATE, lutetium-177-DOTA0-Tyr3-octreotate; CT, computed tomography; DFS, disease-free survival; EFS, event-free survival; M, MYC-associated factor X; MRI, magnetic resonance imaging; NF1, neurofibromin 1; OS, overall survival; PC, pheochromocytoma; PET/CT, positron emission tomography/computed tomography; PGL, paraganglioma; Ret, rearranged during transfection; SDHA, succinate dehydrogenase complex flavoprotein subunit A; SDHAF2, succinate dehydrogenase complex assembly factor 2; SDHBI, succinate dehydrogenase complex iron sulfur subunit B; SDHC, succinate dehydrogenase complex subunit C; SDHD, succinate dehydrogenase complex subunit D; TMEM127, transmembrane protein 127; TREP, Tumori Rari in Età Pediatrica—rare tumors in pediatric age; VHL, von Hippel-Lindau.
1 | INTRODUCTION

Pheochromocytomas and paragangliomas (PCs/PGLs) are rare catecholamine-producing tumors that may arise, respectively, from the adrenal medulla or extra-adrenal ganglia along the sympathetic/parasympathetic chains (chromaffin or nonchromaffin origin). Their incidence varies from 0.2-0.3 to 2 cases per million children per year.1,2 Symptoms are related to the catecholamine hypersecretion, and diagnosis is based on the determination of plasma and urinary metanephrines (sometimes catecholamines), radiological characterization, and functional imaging tests.3 Although in most cases they are sporadic, they may be also part of a more complex hereditary syndrome. Actually PC/PGL are more commonly associated with an inherited mutation than any other cancer type, and these mutations normally involve genes such as von Hippel-Lindau (VHL), rearranged during transfection (Ret), neurofibromin 1 (NF1), SDH-x, and MYC-associated factor X (MAX).4 Over one third of patients with paraganglial tumors carry germline mutations in one of the ten susceptibility genes: VHL, Ret, NF1, succinate dehydrogenase complex assembly factor 2 (SDHAF2), succinate dehydrogenase complex flavoprotein subunit A (SDHA), succinate dehydrogenase complex iron sulfur subunit B (SDHB), succinate dehydrogenase complex subunit C (SDHC), succinate dehydrogenase complex subunit D (SDHD), MAX, and transmembrane protein 127 (TMEM127).5-11 Surgery remains the main curative treatment.12 Due to the rarity of these tumors in children, their genetic and biologic characteristics are still not well defined. On the other hand, diagnostic and therapeutic guidelines do exist for familial forms and they may be of help during screening and surveillance of this subset of PC/PGL.13

The purpose of this study is to analyze the clinical findings, treatment, and outcome observed in pediatric patients (age < 18) with PC/PGL, registered in our National Study on Rare tumors in children (Tumori Rari in Età Pediatrica—Rare Tumors in Pediatric Age (TREP) project), in order to evaluate the efficacy of our clinical, diagnostic, and therapeutic approach, and to offer a contribution to literature on these tumors.

2 | MATERIALS AND METHODS

The TREP project, launched and approved by the local ethics committee in 2000, represents the first Italian multi-institutional network on very rare tumors in children and adolescents (age < 18). The histotypes registered are those with an incidence of less than two cases per 1 million children, and not treated in current national or interna-

Conclusions: Surgery can be curative in most tumors but it may not be always effective in removing PGLs. Severe postsurgical sequelae may affect these patients. Genetic tests should always be considered in individuals affected, and genetic counseling should be offered to their families.

KEYWORDS

children, paraganglioma, pheochromocytoma, rare cancer
### TABLE 1  Clinical features of 28 patients with PC

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (months)</td>
<td>150.5 (Mean 146.6)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>19 (67.8%)</td>
</tr>
<tr>
<td>Females</td>
<td>9 (32.1%)</td>
</tr>
<tr>
<td>Germline mutation</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>15 (53.6%)</td>
</tr>
<tr>
<td>Negative</td>
<td>11 (39.3%)</td>
</tr>
<tr>
<td>Not tested</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Surgical approach</td>
<td></td>
</tr>
<tr>
<td>Open</td>
<td>18 (64.3%)</td>
</tr>
<tr>
<td>VLS</td>
<td>10 (35.7%)</td>
</tr>
<tr>
<td>Resection</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>26 (92.9%)</td>
</tr>
<tr>
<td>With residuals</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Catecholaminergic</td>
<td>20 (71.4%)</td>
</tr>
<tr>
<td>Incidental diagnosis or screening</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (3.5%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Side at diagnosis</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>12 (42.9%)</td>
</tr>
<tr>
<td>Left</td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td>Bilateral</td>
<td>3 (10.7%)</td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>14 (50%)</td>
</tr>
<tr>
<td>≥5 cm</td>
<td>12 (42.9%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Secreting status</td>
<td></td>
</tr>
<tr>
<td>Secreting</td>
<td>22 (78.6%)</td>
</tr>
<tr>
<td>Not secreting</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (14.3%)</td>
</tr>
<tr>
<td>Conventional imaging</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>15 (53.6%)</td>
</tr>
<tr>
<td>MRI</td>
<td>13 (46.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (7.1%)</td>
</tr>
<tr>
<td>Functional imaging</td>
<td></td>
</tr>
<tr>
<td>$^{123}$I-MIBG scintigraphy</td>
<td>11 (7)</td>
</tr>
<tr>
<td>PET/CT (1 $^{18}$F-DOPA, 1 $^{18}$F-FDG, 1 $^{111}$In-Pentreotide)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>Median 54</td>
</tr>
<tr>
<td></td>
<td>Mean 58.9</td>
</tr>
</tbody>
</table>

Abbreviations: $^{123}$I-MIBG, $^{123}$iodium-metaiodobenzylguanidine; MRI, magnetic resonance imaging.

*The number of altered functional imaging are in parentheses.

### TABLE 2  Clinical features of 22 patients with PGL

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (months)</td>
<td>143.5 (Mean 148.1)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>14 (63.6%)</td>
</tr>
<tr>
<td>Females</td>
<td>8 (36.4%)</td>
</tr>
<tr>
<td>Germline mutation</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>10 (45.5%)</td>
</tr>
<tr>
<td>Negative</td>
<td>7 (31.8%)</td>
</tr>
<tr>
<td>Not tested</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Resection</td>
<td></td>
</tr>
<tr>
<td>Complete</td>
<td>10 (45.6%)</td>
</tr>
<tr>
<td>With residuals</td>
<td>12 (54.4%)</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
</tr>
<tr>
<td>Catecholaminergic</td>
<td>15 (68.1%)</td>
</tr>
<tr>
<td>Mass effect</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Incidental diagnosis</td>
<td>4 (18.2%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (22.7%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>16 (72.2%)</td>
</tr>
<tr>
<td>Head and neck</td>
<td>2 (9.1%)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>&lt;5 cm</td>
<td>12 (54.4%)</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>10 (45.6%)</td>
</tr>
<tr>
<td>Secreting status</td>
<td></td>
</tr>
<tr>
<td>Secreting</td>
<td>9 (41%)</td>
</tr>
<tr>
<td>Not secreting</td>
<td>12 (54.4%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Conventional imaging</td>
<td></td>
</tr>
<tr>
<td>CT</td>
<td>19 (86.4%)</td>
</tr>
<tr>
<td>MRI</td>
<td>11 (50%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (4.5%)</td>
</tr>
<tr>
<td>Functional imaging</td>
<td></td>
</tr>
<tr>
<td>$^{123}$I-MIBG scintigraphy</td>
<td>13 (2)</td>
</tr>
<tr>
<td>PET/CT (2 $^{18}$F-FDG, 2 $^{67}$Ga-DOTATOC, 4 $^{18}$F-DOPA)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>$^{99}$Tc scintigraphy</td>
<td>3 (0)</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>Median 55</td>
</tr>
<tr>
<td></td>
<td>(Mean 61.3)</td>
</tr>
</tbody>
</table>

Abbreviations: $^{67}$Ga-DOTATOC, $^{67}$Ga-DOTA-Phe1-Tyr3-octreotide; $^{123}$I-MIBG, $^{123}$iodium-metaiodobenzylguanidine; MRI, magnetic resonance imaging.

*The number of altered functional imaging are in parentheses.
In all cases, computed tomography (CT) scan or magnetic resonance imaging (MRI) was useful to detect or assess the tumors. $^{123}$I-iodiometaiodobenzylguanidine ($^{123}$I-MIBG) scintiscan was additionally performed in 11 cases and in 7 was altered. One patient underwent fluorine-18-L-dihydroxyphenylalanine ($^{18}$F-DOPA) positron emission tomography/computed tomography (PET/CT) scan, which confirmed the diagnosis and revealed an asymptomatic bone metastasis in the thoracic spine.

### 3.1.2 Paragangliomas

Twenty-two patients had PGL. Ten of 22 children had a germline mutation: two children had VHL syndrome, six had hereditary PGL/PC type 1 syndrome (SDHB), and two had hereditary PGL/PC type 4 syndrome (SDHD). The genetic tests were not performed in five patients (in one case due to parents' opposition). In 15 cases the main symptom was hypertension, associated with headache, diaphoresis, fever, dyspnea, gastrointestinal, and visus disorders. One patient also had chest pain and 2 of 13 presented with acute heart failure due to hypertensive cardiomyopathy. In three patients, the tumor was detected incidentally and in one of them during assessment for a familial syndrome. Two patients with head-and-neck PGL had symptoms related to tumor mass effect (tinnitus, hypoacusia, earache, palpable mass in the temporal region); one patient had nonspecific abdominal pain, and one had pelvic PGL, metrorrhagia.

Data on urinary and plasmatic markers were available in 21 of 22 children, but only 9 (41%) had altered catecholamines and/or methanephrines levels.

A scintiscan with $^{123}$I-MIBG was performed in 13 of 22 patients, and was altered in two cases only, whereas PET/CT scan, performed in eight patients (two fluorine-18-fluorodeoxyglucose ($^{18}$F-FDG), four $^{18}$F-DOPA, two $^{67}$Ga-DOTA-Phe1-Tyr3-octreotide), was altered in all cases.

### 3.2 Treatment

All patients eligible for surgery and with secreting tumors or signs of hypertensive disease were pharmacologically treated with adrenergic antagonists (doxazosin or prazosin), which were started at 6-8 weeks after diagnosis and continued during follow-up. In 6 cases, the dose of the adrenergic blocker was increased (up to 2.5 mg/d). The mean interval between diagnosis and the start of the adrenergic therapy was 5.4 months (range 1-20 months).

In 20 children, a multimodal therapy was performed: sandostatin, and an autologous stem cell transplant. In both cases it was difficult to assess the response to chemotherapy, since the tumors were in advanced stage. In 6 cases, surgery was not feasible. In one case, the patient with a locally invasive PGL of the middle cranial fossa underwent biopsy and angiographic embolization before surgery, in order to reduce the mass volume.

### 3.3 Relapses, metachronous tumors, and outcome

#### 3.3.1 Pheochromocytomas (see Table 3 for details)

Relapses and metachronous tumors occurred in 6 of 28 patients after a mean period of 59 months (range 3-132 months); all had a palliative approach was utilized overall in 10 patients and in 2 of them conversion to open surgery was necessary. After surgery, one patient received external radiotherapy on her spinal metastasis.
## TABLE 3  Clinical features of patients with relapse or metachronous tumors

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at diagnosis (in months)</th>
<th>Sex</th>
<th>Syndrome</th>
<th>Site</th>
<th>First treatment</th>
<th>Re or mT (months from the previous treatment)</th>
<th>Treatment of the relapse</th>
<th>Outcome (FU months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC1</td>
<td>215</td>
<td>M</td>
<td>MEN 2A</td>
<td>Left adrenal gland</td>
<td>Left adrenalectomy (MIS)</td>
<td>PC on the right adrenal gland (120)</td>
<td>Adrenal-sparing tumorectomy</td>
<td>2nd CR (48)</td>
</tr>
<tr>
<td>PC2</td>
<td>129</td>
<td>F</td>
<td>Familial paraganglioma type 4 (SDHB)</td>
<td>Left adrenal gland</td>
<td>Left adrenalectomy</td>
<td>Liver metastases (96)</td>
<td>Radiometabolic therapy (ongoing with lutetium-177-DOTA(^{177})-Tyr(^{3})-octreotate)</td>
<td>AWD (8)</td>
</tr>
<tr>
<td>PC3</td>
<td>77</td>
<td>M</td>
<td>VHL</td>
<td>Left adrenal gland</td>
<td>Adrenal-sparing tumorectomy + interaortocaval node resection (MIS)</td>
<td>1. Interaortocaval lymphadenectomy 2. Adrenal-sparing tumorectomy (MIS) 3. Right adrenalectomy and left pararenal node resection + TM 4. Radiometabolic therapy (ongoing with lutetium-177-DOTA(^{177})-Tyr(^{3})-octreotate)</td>
<td>AWD (6)</td>
<td></td>
</tr>
<tr>
<td>PC4</td>
<td>153</td>
<td>M</td>
<td>VHL</td>
<td>Right adrenal gland</td>
<td>Adrenal-sparing tumorectomy</td>
<td>1. Right adrenal gland (9) 2. Left adrenal gland and interaortocaval nodes (26) 1. Right adrenalectomy 2. Left adrenalectomy + interaortocaval lymphadenectomy + radiometabolic therapy (MIBG)</td>
<td>3rd CR (84)</td>
<td></td>
</tr>
<tr>
<td>PC5</td>
<td>83</td>
<td>F</td>
<td>VHL</td>
<td>Right adrenal gland</td>
<td>Right adrenalectomy</td>
<td>Left adrenal gland (132)</td>
<td>Left adrenalectomy</td>
<td>2nd CR (12)</td>
</tr>
<tr>
<td>PC6</td>
<td>170</td>
<td>M</td>
<td>VHL</td>
<td>Right adrenal gland</td>
<td>Adrenal-sparing tumorectomy</td>
<td>Left adrenal gland (4)</td>
<td>Adrenal-sparing tumorectomy (MIS)</td>
<td>2nd CR (5)</td>
</tr>
<tr>
<td>PGL1</td>
<td>124</td>
<td>M</td>
<td>Familial paraganglioma type 4 (SDHB)</td>
<td>Right retroperitoneum</td>
<td>Complete excision</td>
<td>Diffuse bone metastases (120)</td>
<td>None (wait and see)</td>
<td>AWD (54)</td>
</tr>
<tr>
<td>PGL2</td>
<td>133</td>
<td>F</td>
<td>Not tested</td>
<td>Right pelvis</td>
<td>Excision with microscopic residuals</td>
<td>Local relapse (4)</td>
<td>Neoadjuvant chemotherapy (IFO, VP-16, VCR, ADM, CP, CBDCA), debulking, adjuvant chemotherapy (VP-16, ADM), auto-SCT, excision of the residual disease</td>
<td>2nd CR (122)</td>
</tr>
<tr>
<td>PGL3</td>
<td>130</td>
<td>M</td>
<td>VHL</td>
<td>Right retroperitoneum</td>
<td>Complete excision</td>
<td>Bilateral adrenal glands (48)</td>
<td>Right adrenalectomy and left adrenal sparing tumorectomy</td>
<td>2nd CR (lost)</td>
</tr>
<tr>
<td>PGL4</td>
<td>144</td>
<td>f</td>
<td>None</td>
<td>Left pelvis</td>
<td>Excision with microscopic residuals</td>
<td>Local relapse (40)</td>
<td>Debulking + chemotherapy (ADM, VP-16 and CDDP)</td>
<td>AWD (48)</td>
</tr>
</tbody>
</table>

Abbreviations: ADM; Adriamycin; AWD, alive with disease; CBDCA; carboplatin; CDDP; cisplatin; CP, Cyclophosphamide; CR, complete remission; IFO, Ifosfamide; MIS, mini-invasive surgery; mT, metachronous tumors; PGL, paraganglioma; Re, relapses; SCT; stem cell transplant; TMZ, temozolamide; VCR, vincristine; VHL, von Hippel-Lindau; VP-16, etoposide; \(^{123}\)I-MIBG, \(^{123}\)iodine-metaiodobenzylguanidine.

Familial syndrome (four had VHL syndrome, one had MEN 2A syndrome, and one had PGL/PC type 1 syndrome) and 3 of 6 patients had previously undergone laparoscopic surgery. Three patients (two with VHL syndrome and one with MEN 2A) who underwent unilateral adrenalectomy developed contralateral tumors: all were treated with surgery and in two cases a partial adrenalectomy was feasible. Two patients with VHL syndrome developed multiple local, contralateral, and distant relapses (nodes and paraganglia): one received multiple...
resections and $^{123}$I-MIBG metabolic therapy and reached a third com-
plete remission; one, despite multiple surgeries to the contralateral
adrenal gland, nodes, and paranganglial relapses, developed diffuse
metastatic disease (liver, lung, bones, and distant nodes). Another
patient developed liver metastases 8 years after the first surgery and
is currently in the charge of an adult center. The latter two patients
are currently receiving ongoing radiometabolic therapy based on
lutetium-$^{177}$DOTA-Tyr$^3$-octreotate ($^{177}$Lu-DOTATATE).

At the time of this report, all patients are alive, 26/28 in complete
remission and two with disease (overall survival [OS] 100%; event-free
survival [EFS] 79%); four of them are suffering from adrenocortical
failure. Mean follow-up was 58.9 months (range: 2-156 months); four
patients were lost to follow-up while in complete remission.

### 3.3.2 Paragangliomas (see Table 3 for details)

Relapses occurred in four of 22 patients after a mean period of 52
months (range: 3-120 months); two of four occurred in patients who
underwent incomplete tumor resection and only two of four had a
germline mutation. One patient with VHL syndrome and a right
pararenal PGL, who underwent complete tumor resection, developed
ipsilateral recurrence and left paravertebral metastasis and required
right adrenalectomy and partial left adrenalectomy. Two patients with
locally invasive pelvic PGL developed multifocal recurrence: in one
case, the relapse was treated with chemotherapy and the patient was
alive with minimal stable disease; in the other case relapse was treated
with neoadjuvant chemotherapy, surgery (with microscopic residuals),
adjuvant chemotherapy followed by autologous stem cell transplanta-
tion, and demolitive surgery on the residual disease. The latter patient
was able to achieve a second remission. One patient, affected by a com-
pletely resected retroperitoneal PGL, experienced diffuse bone metas-
tases 10 years after surgery and he is being treated with a wait-and-
see strategy at the time of this report. The patient with unresectable
mediastinal PGL received further chemotherapy after mass growth,
but died while receiving palliative care.

At the time of this report, 18 patients are alive in complete remis-
sion (3/18 lost at follow-up), but 2 with severe sequelae: 1 patient
developed first bite syndrome and Claud-Bernard-Horner syndrome
and 1 patient developed neurogenic bladder after mutilating surgery.
Three patients are alive with stable disease (1/3 opted out) and one
patient died of disease (OS 95%; EFS 77%). Mean follow-up was 61.3
months (range: 0-168 months).

### 3.4 Pathology

Pheochromocytoma of the adrenal gland-scaled score (PASS) was
available in the original pathology report in 14 of 28 patients with PC
and in 8 of 22 patients with PGL. The score was reported to be >4
in four of 14 patients with PC and in five of eight patients with PGL.
Among the patients with a malignant appearance at histology, only one
patient with PGL (with familial PGL/PC type 4) experienced a recur-
rent disease, while the other two patients with PGL presented with a
bone metastasis at diagnosis in one case (negative for germine muta-
tion; in first CR) and a locally invasive tumor in the other case (opted
out in alive with disease status and not tested). In the benign group,
recurrent disease occurred in four patients with PC (all with a germline
mutation: two with VHL syndrome, one with MEN 2A syndrome, and
one with familial PGL/PC type 4) and in one patient with PGL (with VHL
syndrome).

### 3.5 Statistical analysis

EFS curves and cumulative risk curves (Figures 1 and 2) according
Kaplan-Meier method were built and tested with log-rank (Mantel-
Cox): $P$ values of <0.05 were considered significant. Univariate
analysis, performed by grouping PC and PGL together, showed no
statistically significant difference in EFS for the presence of a germine
mutation, the completeness of surgery, the sex of the patient, and the
age at diagnosis.

### 4 DISCUSSION

PC/PGL are rare tumors, however information on the exact incidence
in children and adolescents is missing. This is particularly true for
tumors affecting adolescents, mostly observed and treated in centers
for adults. After the launch of the TREP project, Pastore et al. under-
lined a remarkable increase in the enrolment of patients between the
ages of 0 and 14 years; however, the real incidence is difficult to deter-
mine without the involvement of the adult centers.\(^\text{14,15}\)

A diagnosis of PC/PGL is often not simple: for PC, the differential
diagnosis includes neuroblastoma, a more frequent tumor in children,
and adrenocortical tumor, which is also very rare, but with different
clinical characteristics. Thus, adrenal masses should be properly
evaluated, with an accurate analysis of the clinical features and serum
and urinary markers, and the proper selection of conventional and
functional imaging. CT scan and MRI have been demonstrated to be
equally useful to describe the radiological aspects of the tumor, the
size, the involvement of vital structures, and possibly define a proper
operative approach. In recent years, both $^{18}$F-FDG and $^{18}$F-DOPA
PET/CT have demonstrated to be the gold standard in providing a
more accurate staging\(^\text{\textsuperscript{123-131}}\). MIBG is considered to perform equally
well in localized cases), and additional information regarding metabolic
activity and biologic aggressiveness of these tumors to possibly guide
treatment choices.\(^\text{1,3,16}\)

A complete preoperative workup should include genetic counseling
because one third of patients with paranganglial tumors carry germine
mutations in one of the susceptibility genes: RET, VHL, NF1, SDHAF2,
SDHA, SDHB, SDHC, SDHD, TMEM127, and MAX. In our series, 43 of
50 patients were evaluated for a germinle mutation, and in 25 cases
(>50%) tumors were associated with an inherited mutation. Among
them, three tumors arose in patients who already had a diagnosis of an
inherited mutation (two with PC, one with PGL). Most of the remaining
patients were tested for VHL syndrome, familial PGL syndromes, and
MEN syndromes: in 14 of them a diagnosis of a cancer-predisposing
syndrome was possible, and it is remarkable how in 6 of them a positive
familial history was also present. As previously reported,\(^\text{4,6,17}\) SDHB
resulted to be the most frequent mutated gene in patients affected by PGL, while VHL the most frequent in patients with PC.

The rate of tumors arising in syndromic patients is yet to be clearly defined: recently, some authors\(^1,3\) reported up to 80% of genetic mutations in their series, comparing them with lower proportions in previous reports (22-70%).\(^2,5,18-20\) The difference in the prevalence rate of germline mutations in the various series, including ours, may be due to a selection bias,\(^1\) which reflects the fact that children with a positive familial history of FC/PGL may sometimes be treated outside pediatric centers. As one may deduce, a reliable estimate of the prevalence rate of syndromic PC/PGL on the total amount of pediatric PC/PGL cases could be definitely ruled out only by international prospective studies or tumor registries. Of course, all authors agree to recommend that all patients presenting with a PC/PGL, with or without a positive family history, should undergo genetic testing.\(^1,4\)

The surgical approach for a PC should be planned according to the secretion status of the tumor, the presence of bilateral lesions, and surgeon’s experience. Special attention moreover should be given to children with an inherited syndrome who could benefit of a cortical-sparing surgery since a metachronous contralateral tumor may develop, and thus avoid the risk of future adrenal failure.\(^21-23\)

Before surgery, all patients with a secreting PC should be treated with alpha-blockers in order to avoid the risk of potentially fatal catecholamine storms\(^24\): this treatment usually lasts for 2-4 weeks, and
the patient needs to be carefully monitored before, during, and after surgery. Even if some authors questioned the use of alpha-blockers preoperatively when a mini-invasive approach is planned, pretreating hypertension seems so far the most reasonable approach.26,27

A mini-invasive approach is feasible but it should be performed preferably in tertiary centers with high volumes of oncologic cases and laparoscopic procedures in the pediatric population.24,25,28 This is justified in order to minimize the possible onset of severe intraoperative complications (such as severe bleeding) and to maximize the benefit of laparoscopic surgery. Moreover, the possible need of intensive postoperative monitoring should be taken into consideration.

The different localizations of PGL require a multidisciplinary discussion among different specialists who should always be involved on the basis of the tumor site and invasiveness (ear, nose, and throat surgeons; vascular surgeons; and interventional radiologists), with the aim to perform a complete resection, avoiding severe surgical sequela. In two patients in our series, angiographic embolization was used to reduce the mass before the surgery in one case and in association with systemic therapy to treat an unresectable mass in another case. The use of alternatives to surgical excision (angiographic embolization, radiofrequency ablation, or cryoablation) has been mostly described for metastatic PC/PGL.39 A recent systematic review underlined how ablation techniques have been used in adults with different aims (palliative care, symptom control, or treatment of unresectable lesions, with or without other associated systemic/local therapies), while, in the pediatric age group, their application is still anecdotal.32,33

As reported before, the use of chemotherapy and its efficacy are difficult to determine, since patients who received medical treatment were inoperable or presenting with multiple relapses. Similarly, this is true for radiotherapy and radiometabolic therapy, even though some relapsed patients seemed to benefit from a multimodal approach. Thus, the most commonly used radiometabolic treatment is 131I-MIBG, and promising results seem to come from the use of 177Lu-DOTATATE. In our series, only two patients were eligible for 177Lu-DOTATATE, but the response has not yet been evaluated, since their treatment is ongoing.

The outcome in our series is apparently better than the previous reported experiences, especially as concerns patients affected by PC. PGLs seem to have a worse prognosis, and this may be due to late diagnosis, site and local invasiveness: since they arise from paraganglia, these tumors grow along major vessels, encasing them in some cases, making an R0 resection difficult to be obtained (as similarly seen in childhood neuroblastoma surgery). This difficulty to obtain a complete surgical resection could be considered one main prognostic factor in the PGL subgroup.

Some studies observed a significantly higher rate of relapse in patients with a germline mutation, but this observation was not confirmed by our findings. Despite 8 of 10 patients who experienced a relapse being carriers of a germline mutation, and an apparent difference in the cumulative risk curves, the analysis did not reach statistical significance. This may be due to different reasons: low number of patients, heterogeneity in follow-up duration, different features of the two subgroups examined (PC and PGL), and the nature of the registry itself. In particular, absent or less prolonged follow-up of pediatric patients suffering from a familial PC/PGL and who may present with a relapse or a metachronous tumor later in life, have been suggested to explain this issue.38

However, several studies underlined the importance of careful follow-up especially in carriers of VHL and SDHD mutations because of their predisposition to develop recurrences or metachronous tumors.4,13,39,40 Reasonably, the subset of patients with a proven germline mutation should be followed for a longer time period and managed properly until adult care transition.

In conclusion, PC/PGL represents a group of neoplasms whose care raises several issues and strongly requires a multidisciplinary approach: the diagnostic process, treatment, and follow-up for children affected may represent a challenge for all the physicians involved. It is highly desirable that all pediatric patients affected may be referred to and treated in pediatric tertiary centers, where they can find all the necessary specialists and appropriate investigations. Moreover, as for other very rare tumors, it seems quite urgent to make registries go beyond national borders and create larger prospective international studies to achieve more information on epidemiology and a better knowledge of the clinical and genetic characteristics of these tumors.

CONFLICT OF INTEREST
The authors declare that there is no conflict of interest.

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DATA AVAILABILITY STATEMENT
The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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