International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

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ARTICLE TITLE	PHEOCHROMOCYTOMA AND PARAGANGLIOMA: CLINICAL PICTURE, DIAGNOSIS, TREATMENT, FOLLOW-UP AND PROGNOSIS - A LITERATURE REVIEW
DOI	https://doi.org/10.31435/ijitss.3(47).2025.4008
RECEIVED	09 August 2025
ACCEPTED	28 September 2025
PUBLISHED	30 September 2025
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PHEOCHROMOCYTOMA AND PARAGANGLIOMA: CLINICAL PICTURE, DIAGNOSIS, TREATMENT, FOLLOW-UP AND PROGNOSIS - A LITERATURE REVIEW

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ABSTRACT

Introduction and aim: Pheochromocytoma and paraganglioma (PPGL) are tumors of chromaffin cells. The incidence of this disease is 2 to 8 cases per million. The peak incidence occurs in the 3rd to 5th decade of life. This article aims to review reports on the clinical picture, diagnosis, treatment, follow-up and prognosis of PPGL.
State of knowledge: Excess catecholamines secreted by the tumor can cause symptoms such as headache, sweating, hypertension, heart palpitations, and can also lead to organ damage. The diagnosis of PPGL includes the assessment of the clinical picture, biochemical tests, imaging studies, family history and genetic tests. The first-line test in the diagnosis is the determination of free methoxy-catecholamines concentrations in plasma. Surgical excision is the primary treatment for most localized PPGLs. To minimize the risk of perioperative cardiovascular complications in patients with pheochromocytoma and hormonally active paraganglioma, preoperative adrenergic receptor blockade is recommended. A minimum of 10 years of annual follow-up is recommended for every patient with a resected PPGL. When radical treatment is not possible, the therapeutic goals shift towards slowing down tumor progression and maintaining quality of life. The strongest predictor of a poor prognosis is the presence of metastases at diagnosis.
Conclusions: PPGLs are clinically challenging diagnoses. It is important to evaluate the diagnosis and treatment in a multidisciplinary team. Treatment should be tailored to each patient individually to protect against side effects and ensure a favorable prognosis. Further research is needed to increase the chances of early diagnosis and improve patient outcomes.

KEYWORDS

Pheochromocytoma, Paraganglioma, Catecholamines, Diagnosis, Treatment

CITATION

Dominika Żyła, Kornelia Rojek, Andrzej Zuzak, Katarzyna Zych, Sylwia Koziej, Adam Jakubas, Mateusz Korga, Milena Krawczyk. (2025) Pheochromocytoma and Paraganglioma: Clinical Picture, Diagnosis, Treatment, Follow-Up and Prognosis – A Literature Review. *International Journal of Innovative Technologies in Social Science*. 3(47). doi: 10.31435/ijitss.3(47).2025.4008

1. Introduction and Aim

Pheochromocytomas and paragangliomas (together referred to as PPGLs) are rare tumors that develop from chromaffin cells. Pheochromocytoma (PCC) is located in the adrenal medulla, while paraganglioma (PGL) originates from extra-adrenal sympathetic paragangliomas [1]. PPGLs can produce, secrete and store catecholamines as well as other substances, for example: VIP, ACTH, CRH, PTH- and calcitonin-related peptides, opioids, histamine, interleukin-6, chromogranin, etc. They have a low clinical awareness despite a prevalence of 1 in 500-1000 people with hypertension, and an increasing incidence due to more frequent imaging studies and better detection of catecholamine metabolites [2]. The total annual incidence of PPGL is estimated at 2 to 8 cases per million. PPGL is most common between the 3rd and 5th decades of life and approximately 10% to 20% occur in pediatric patients [3,4]. About 25% of PPGL cases have a genetic basis, and 50% of these patients have a pathogenic germline variant [2]. PPGLs are associated with germline and/or somatic mutations in more than 20 genes [5]. These mutations are divided into three molecular clusters: pseudohypoxia cluster 1A and 1B, kinase-signaling cluster 2, and Wnt signaling cluster 3 [6]. Genetic syndromes such as multiple endocrine neoplasia type 2 (MEN 2), von Hippel–Lindau (VHL) syndrome, and neurofibromatosis type 1 (NF1) are associated with an increased risk of developing PCC [7]. This increasing genetic understanding is driving advancements in personalized management, integrating various modalities for tailored diagnosis, treatment, and follow-up strategies [6]. The most common clinical symptom of the tumor is systemic arterial hypertension (SAH), which occurs in 90% of cases [2]. PPGLs can be "clinically silent", characterized by the absence of typical hypertension, and are increasingly recognized due to incidental findings on imaging and surveillance programs for genetic syndromes. Several factors contribute to this silent presentation, including small tumor size and the type and pattern of secreted catecholamines [8]. The diagnosis of PPGL is based on the finding of elevated plasma or urinary metanephrines [9]. Imaging plays a crucial role in the management of PPGLs, including diagnosis, localization, staging, evaluation of treatment response, surveillance, and selection for specific therapies [10]. In case of locoregional disease, the primary treatment is

surgery, with minimally invasive adrenalectomy being preferred. For head and neck PGLs, management depends on various factors and may include observation, surgery or radiation therapy. Preoperative management for catecholamine-secreting PPGLs includes α-adrenergic receptor blockade to prevent hypertensive crises [6]. The aim of this article is to review reports on PPGL, its clinical picture, diagnosis, treatment, follow-up and prognosis.

2. Materials and Methods

A literature review was conducted using PubMed, Scopus, Web of Science and Google Scholar databases. The following search terms and their combinations in English were used when reviewing the databases mentioned above: "PHEOCHROMOCYTOMA", "PARAGANGLIOMA", "DIAGNOSIS", "TREATMENT", "PPGL" and the operator "AND". The analyzed publications about PPGLs were dated from 2010 to 2024. Three of the studies with publication dates of 1968, 1977 and 1983 were considered key reports on PPGL. Due to their high merit and relevance to the topic at hand, they were included in the review. Selected papers on the clinical picture, diagnosis, treatment, follow-up and prognosis of PPGL were analyzed. A total of 74 articles were used for the review.

3. State of Knowledge

3.1. Clinical Picture

Excessive secretion of catecholamines by PPGLs causes various symptoms such as hypertension, headache, diaphoresis, palpitations and also leads to damage to many organs, including catecholamine-induced cardiomyopathy [11]. SAH is the most common clinical manifestation of PPGL, but the most characteristic findings of this disease are paroxysms (headache, sweating and palpitations). Paroxysms occur with an unpredictable frequency, ranging from a single episode every 2-3 months to 30 times a day, and last from a few minutes (usually 15 to 60 minutes) to days [2]. Paroxysmal symptoms may appear spontaneously or may be caused by triggering factors such as large meals, abdominal pressure, exercise, medications (e.g., glucocorticosteroids, metoclopramide, antidepressants, some anesthetics), food (e.g., tyramine in some cheeses), stress, and alcohol [12]. PGLs arising in the parasympathetic tissue of the head and neck are usually silent (i.e., they do not secrete any catecholamines) [13]. Head and neck PGLs can lead to symptoms resulting from compression or invasion of adjacent structures, such as dysphagia, hearing loss, cranial nerve palsies, and pulsatile tinnitus [12,14]. In 30-40 % of cases, PPGLs are associated with mutated genes (e.g., RET, VHL, NF1, SDHx, TMEM127, MAX), which increases the risk of the disease and its early manifestation in those with a family history of burden [15,16]. Unexpected acute neurological symptoms such as posterior reversible encephalopathy syndrome (PRES), seizures and renal hypertension have been reported in children with PGL - these symptoms are non-hormonal but severe manifestations of the disease [17,18]. Cases of interleukin-6 secreting tumors (both PCC and PGL) have also been described, presenting with persistent fever, elevated inflammatory markers and systemic inflammatory response syndrome (SIRS) symptoms, despite the absence of typical catecholamine symptoms [19,20]. Increased catecholamine release from PPGLs can cause life-threatening cardiovascular manifestations, such as acute heart failure, hypertensive crisis, tachy- and bradyarrhythmias, myocardial infarction, and Takotsubo cardiomyopathy [12,21]. Rare cases of patients with PCC who develop dangerous arrhythmias such as torsades de pointes and QT prolongation without previous symptoms are presented [22,23]. One rare but potentially fatal complication is catecholamine crisis, which leads to rapid hemodynamic instability with organ damage and is associated with a mortality rate of around 15% [24].

3.2. Diagnosis

The diagnosis of PPGL includes a number of procedures such as evaluation of the clinical picture, biochemical tests, imaging studies to visualize the location and local extent of the tumor, family history and genetic testing.

The primary diagnostic step is to perform laboratory tests. The first-line test is to assess the plasma concentration of free methoxy-catecholamines such as methoxy-noradrenaline, methoxy-adrenaline and methoxy-tyramine. Methoxy-catecholamines reach higher concentrations than catecholamines and have a longer half-life. The test should be carried out under appropriate conditions - in the supine position, fasting and after resting for at least 30 minutes [25,26]. This is followed by an assessment of the excretion of fractionated methoxy-catecholamines in a daily urine collection. Both free metabolites in plasma and urine have near-maximum negative predictive values (>99%) with similar specificity (94%). Sometimes it is also

possible to determine catecholamines - epinephrine, norepinephrine and dopamine - in the daily urine collection, but this method is less sensitive and less specific than others [12].

It is also important to be aware of the medications being taken, as some drugs - such as MAO inhibitors, ephedrine, cocaine, tricyclic antidepressants, serotonin reuptake inhibitors, morphine, amoxicillin, levodopa, sulfasalazine, acetaminophen, methyldopa, and buspirone - can cause false positives [27]. Plasma concentrations of methoxy-catecholamines exceeding twice the upper limit of the reference range indicate a high probability of PPGL, and further imaging studies are recommended. In patients with inconclusive results, a catecholamine suppression test with clonidine is indicated [28]. Three hours after clonidine administration, the absence of a decrease in plasma methoxy-catecholamine levels confirms the presence of a hormonally active tumor. False-positive results may occur in patients with chronically elevated sympathetic activity, such as those with heart failure or obstructive sleep apnea syndrome [29].

Chromogranin A (CgA) is also used in the diagnosis of neuroendocrine tumors. CgA is a protein produced by so-called chromaffin cells in the adrenal medulla and by β cells in the pancreas [30]. It is a non-specific marker, meaning that its presence does not allow for the identification of a specific cancer type. CgA can be useful as a biomarker for biochemically silent PPGL [31].

Imaging is used to determine tumor location, assess disease progression, and evaluate treatment effectiveness. In diagnostic imaging, computed tomography (CT) is the method of choice [32]. Magnetic resonance imaging (MRI) is used in patients whose tumors are located in the skull base and neck, in patients with contraindications to the use of iodine contrast and ionizing radiation [10,33]. PCC should be suspected upon detection of a well-confined adrenal mass with rapid, intense enhancement, which usually shows cystic and hemorrhagic phenomena, high T2 signal intensity and no macroscopic or microscopic lipids [34]. In the presence of metastases, functional imaging often demonstrates higher sensitivity for tumor detection, particularly due to the high incidence of bone metastases and small soft tissue lesions that are difficult to visualize using conventional imaging methods. Functional diagnostics involve the use of radiopharmaceuticals targeting specific receptors and metabolic pathways characteristic of PPGLs. Commonly used agents include 131I/123I-metaiodobenzylguanidine (MIBG), 6-18F-fluoro-l-3,4-dihydroxyphenylalanine, 18F-fluorodeoxyglucose (18F-FDG) and 68Ga-DOTA-somatostatin analogs [31].

Genetic testing should be performed in all patients to detect predisposing mutations. The most common are mutations in SDH (A/B/C/D/AF2), collectively SDHx. Mutations in VHL, RET, NF1, MAX, TMEM12 and HRAS are most common with PCCs, while mutations in SDHx, FH, PHD1/2 and EPAS1/HIF2A are most common with chaperones. Sporadic PPGLs often have somatic mutations in NF1, VHL, RET and MAX [6,35].

If PCC is suspected, a biopsy is not performed. The primary diagnostic criteria include elevated plasma levels of catecholamine metabolites or increased urinary excretion of catecholamines, along with tumor localization on imaging studies. After tumor resection, histopathological examination is conducted to confirm the final diagnosis. To assess malignancy and the risk of metastasis, histopathological grading systems have been developed, including the Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) and the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) [36,37].

Adrenal PCCs are often diagnosed in patients with hypertension, so the differential diagnosis should consider all conditions associated with increased sympathetic activity [38].

3.3. Treatment

The therapeutic strategy for managing PPGL should be formulated by a multidisciplinary team of experts, with careful consideration of both individual patient characteristics - such as age, functional status, and coexisting medical conditions - and tumor-specific features, including the primary site of the lesion, the extent of local and distant spread, hormonal secretion profile, tumor growth kinetics, functional imaging findings, and genetic background. For the majority of localized PPGLs, surgical excision constitutes the cornerstone of treatment. In patients with PCCs and hormonally active PGLs, this intervention must be preceded by adequate perioperative blockade of catecholamines and comprehensive cardiovascular monitoring to minimize perioperative risks. The optimal timing for surgery, as well as the most effective surgical technique, remains a matter of ongoing clinical debate and individualized decision-making. In cases where the disease is advanced and no longer amenable to surgical intervention, curative treatment is not feasible. Therefore, the primary therapeutic goals shift toward decelerating tumor progression and preserving quality of life. Medical therapy becomes imperative in hormonally active PPGLs to prevent potentially life-threatening events related to catecholamine excess. A broad range of treatment modalities may be employed, tailored to tumor behavior and patient status. These include active surveillance for indolent neoplasms, external beam radiotherapy, radionuclide-based treatments, cytotoxic

chemotherapy, molecularly targeted therapies - such as antiangiogenic tyrosine kinase inhibitors (TKIs) - and peptide receptor radionuclide therapy (PRRT) [12,39-41].

Patients with PPGL are particularly vulnerable to the development of acute cardiovascular complications. In the event of a hypertensive crisis, immediate intravenous administration of agents such as phentolamine, sodium nitroprusside, or nicardipine is indicated. Once hemodynamic stability is achieved, oral phenoxybenzamine titration can be initiated to gradually reach target blood pressure levels. Careful fluid management is essential. Diuretics should generally be avoided unless there is clear evidence of volume overload, and even then, they must be used judiciously. Hemodynamic instability is often managed with vasoactive amines. However, their effectiveness may be compromised by downregulation of sympathetic receptors and, in some cases, may worsen PPGL-related cardiomyopathy. In patients with persistent hypotension unresponsive to pharmacologic measures, mechanical circulatory support (MCS) may be required. A systematic review of 62 patients experiencing severe left ventricular systolic dysfunction—characterized by a median left ventricular ejection fraction (LVEF) of 16% (range 5–32%)—who underwent extracorporeal life support (ECLS) due to intractable pheochromocytoma crisis, reported full recovery of left ventricular function (LVEF >50%) in the majority of cases. Notably, 54 of the 62 patients (87%) survived the episode, underscoring the potential reversibility of PPGL-induced cardiac dysfunction when managed with aggressive supportive therapy [42]. There are also reports documenting successful use of left ventricular assist devices (LVADs) in the management of PPGL-induced heart failure, particularly in the perioperative setting. In contrast, intra-aortic balloon pump (IABP) support has been attempted in patients unresponsive to conventional therapies. However, its efficacy in this context has proven limited [40].

3.4. Preparation for Surgery

Anesthesia, direct tumor manipulation during surgery, tumor biopsy, adrenal venography, and iodinated contrast-enhanced arteriography are all procedures that can provoke excessive catecholamine release in patients with PCCs and functional PGLs. These interventions may precipitate hyperadrenergic symptoms and hypertensive crises, posing significant perioperative risk [39]. To prevent this potentially life-threatening phenomenon, the European Society of Endocrinology recommends that patients with PCC and functional PGL undergo a preoperative preparation period lasting 7 to 14 days. During this time, adrenergic receptor blockers are considered the first-line therapy. Some studies suggest that selective α1-adrenergic receptor blockers may be preferable to non-selective agents, as they are associated with lower preoperative diastolic blood pressure, reduced intraoperative heart rate, and improved postoperative outcomes [12,40,41]. Preoperative adrenergic blockade is recommended for patients with functional PPGLs to reduce the risk of perioperative cardiovascular complications. Although the use of α-adrenergic blockers as part of preoperative preparation has become a widely accepted and almost dogmatic practice, this approach is primarily supported by expert consensus and clinical guidelines rather than high-level evidence. Nonetheless, α-receptor blockade remains a routine component of clinical management in many specialized centers [40,43].

In patients with PPGL, a combined α- and β-adrenergic blockade is commonly employed. α-adrenergic blockade can be achieved using either non-selective or selective adrenergic receptor antagonists. Non-selective blockade typically begins with oral phenoxybenzamine at a dose of 10 mg twice daily, which may be gradually increased up to 1 mg/kg/day depending on patient age and clinical response, with blood pressure titrated toward the lower end of the normal range. For selective α1-adrenergic blockade, doxazosin may be initiated at 2 mg/day and titrated up to 32 mg/day until the target blood pressure is achieved. In addition to pharmacologic preparation, a high-sodium diet and liberal fluid intake are recommended to counteract the catecholamine-induced contraction of blood volume. This strategy helps to reduce the risk of orthostatic hypotension and minimizes the likelihood of severe hypotension following surgical tumor resection [39]. Patients undergoing adrenergic blockade should follow a high-sodium diet - typically around 5000 mg per day - alongside adequate fluid intake, approximately 2.5 liters daily, to prevent severe hypotension following tumor removal. An alternative approach includes administering 1 to 2 liters of intravenous isotonic saline (0.9% NaCl) on the day prior to surgery to ensure optimal intravascular volume status.

To evaluate the adequacy of α-receptor blockade before surgery, Roizen proposed a set of clinical criteria known as the Roizen criteria [44]:

1. Blood pressure should remain below 160/90 mmHg for at least 24 hours prior to the operation.
2. In patients with orthostatic hypotension, systolic and diastolic pressures should remain above 80/45 mmHg.

3. There should be no ST-T wave changes on the electrocardiogram for a minimum of one week before surgery.

4. Ventricular ectopy should be limited to no more than one premature ventricular contraction every five minutes.

The goal should be to maintain blood pressure below 130/80 mmHg in the seated position and no lower than 80/45 mmHg in the standing position. The target heart rate should be 60-70 beats per minute while seated and 70-80 beats per minute while standing [39].

Calcium channel blockers (CCBs) are the most commonly used medications in combination with α-adrenergic receptor antagonists to further improve blood pressure control in patients with PPGL. Some studies consider this class of drugs as the primary choice in the preoperative management of PPGL, particularly for patients with normal blood pressure or mild hypertension, as well as for those experiencing significant side effects from α-antagonists. If blood pressure cannot be adequately controlled with α-adrenergic blockade, an additional CCB may be introduced. Furthermore, CCBs can be used as a standalone treatment in patients with normotension or mild hypertension. Excessive catecholamine release has been shown to cause perioperative cardiovascular instability in patients with PPGL, making the administration of drugs that inhibit catecholamine biosynthesis potentially beneficial in the management of PPGL. Metyrosine, a catecholamine synthesis inhibitor, acts by inhibiting tyrosine hydroxylase, the enzyme responsible for converting tyrosine to dihydroxyphenylalanine, a rate-limiting step in the catecholamine biosynthetic pathway. Consequently, metyrosine has been used as a therapeutic approach for PPGL, particularly in regions where phenoxybenzamine is unavailable. Most studies have reported that the combination of metyrosine and α-adrenergic receptor antagonists leads to better blood pressure control, reduced intraoperative blood loss, and a lower volume of replacement fluids during surgery compared to the traditional α-blocker monotherapy approach [41]. Tyrosine hydroxylase inhibitor metyrosine, which inhibits catecholamine synthesis, should be administered to patients who are intolerant to α-blockers or have hypertension that cannot be controlled with α-blockers and/or CCBs. However, recent data suggest that the use of metyrosine in combination with preoperative phenoxybenzamine may reduce intraoperative hemodynamic instability and postoperative cardiovascular complications. Metyrosine is generally well tolerated, with 33% of patients reporting no adverse effects. The most commonly observed side effects include drowsiness and fatigue, which affect between 19% and 81% of patients [45]. Metyrosine is excreted unchanged by the kidneys, and therefore, caution is advised when administering it to patients with chronic kidney disease. At higher doses (>2 g per day), crystalluria may occur. However, Engleman et al. did not observe this complication in patients treated with a daily dose of 4 g [46]. If crystalluria occurs, it can usually be resolved by reducing the dose of metyrosine. Metyrosine can be safely used in patients with other medical conditions [45]. Metyrosine may reduce dopamine levels, and extrapyramidal symptoms can be observed. The information leaflet indicates that extrapyramidal symptoms may occur in up to 10% of patients, ranging from drooling or difficulty speaking to overt parkinsonism. A psychiatric study that administered metyrosine at a daily dose of 3 g for three weeks reported extrapyramidal symptoms in 100% of patients (n = 10) [45,47]. Preoperative antihypertensive treatment has also been recommended for patients with PPGL and normal blood pressure, as malignant hypertension during surgery has been reported in several cases of biochemically silent PPGL in patients who did not receive preoperative therapy [39,41]. If the heart rate exceeds 100 beats per minute 3-4 days after initiating α-blockade, β-adrenergic receptor blockade should be implemented to control tachycardia. The use of β-adrenergic receptor blockers without prior α-receptor blockade is not recommended due to the potential risk of a hypertensive crisis caused by unopposed α-adrenergic receptor stimulation [41]. Among oral β-adrenergic receptor blockers, the preferred options are metoprolol succinate (with controlled release) or atenolol. When selecting β-blockers for the treatment of catecholamine-induced cardiomyopathy in PPGL, it is important to also consider subtype-specific recommendations: in hypertrophic cardiomyopathy, β-blockers that do not cause vasodilation (such as atenolol, metoprolol, or bisoprolol) are preferred [40].

Propranolol can be started at a dose of 20 mg three times daily, with the possibility of increasing the dose to 40 mg three times daily, depending on heart rate. Atenolol can also be initiated at a dose of 25 mg daily and increased to 50 mg daily. Although there is no data regarding the optimal duration of preoperative treatment, blood pressure and heart rate can be normalized after 7-14 days of therapy. Phenoxybenzamine, β-blockers, CCBs, and doxazosin can be safely used during pregnancy [43].

The primary endpoint (i.e., the median cumulative time outside the target blood pressure range during surgery) was 11.1% (4.3-20.6) in the phenoxybenzamine group compared to 12.2% (5.3-20.2) in the doxazosin group (P = 0.75, r = 0.03). The median total Hemodynamic Instability score was lower in the

phenoxybenzamine group compared to the doxazosin group (38.0 [28.8-58.0] vs. 50.0 [35.3-63.8], P = 0.02, r = 0.20). Maximum systolic blood pressure, cumulative time, and the frequency of systolic pressure >160 mmHg, as well as the number of vasodilators used, were lower in the phenoxybenzamine group [48].

3.5. Surgical Treatment

Surgical resection is the cornerstone of therapy for most localized PPGLs, as it remains the only potentially curative treatment modality. Careful preoperative planning is required to select the most appropriate surgical technique. This includes precise anatomical characterization of the primary tumor location (or tumors, if multifocal) and its spread to adjacent structures and/or distant organs. Mortality rates associated with PPGL resection have decreased significantly, from around 40% in the past to 0–3% in contemporary series [12,39,43].

Total resection of head and neck PGL, indicated in younger patients, typically requires prior embolization and may be performed in one or several stages, depending on the extent of the intradural space (IDS) and/or involvement of the internal carotid artery (ICA). In elderly or frail patients, as well as those with bilateral multifocal lesions or residual disease, observation and watchful waiting strategies or alternative non-surgical treatment options may be considered [39].

Immediate surgical intervention without stabilizing the patient's condition is associated with high morbidity and mortality. These patients should be treated as medical emergencies rather than surgical ones. Many of these patients can be stabilized using α-blockers. However, such patients should be closely monitored and stabilized using a multidisciplinary approach. In rare cases, in order to treat severe cardiogenic shock, an IABP or ECMO may be required, which can significantly contribute to treatment and extend survival. Tumors can be resected within 1-2 weeks in patients who typically recover with medical support and intensive care. However, in very severe cases, immediate surgery may occasionally be required. Additionally, immediate surgery may be necessary in the case of tumor rupture or uncontrolled bleeding [43].

Adrenalectomy can be performed using either laparoscopic or open techniques. Both approaches can be conducted transabdominally or retroperitoneally. Recurrence rates do not differ between the two surgical approaches, with the conversion rate to open adrenalectomy ranging from 5% to 12% [39]. Laparoscopic surgery can be performed conventionally or robotically. The choice of surgical approach depends on the size and type of the lesion, the patient's general characteristics, and the surgeon's experience and preferences. Laparoscopic adrenalectomy has become the gold standard for the treatment of selected patients. Laparoscopic adrenalectomy should not be considered contraindicated even in patients with reversed organ positioning. This minimally invasive procedure results in less intraoperative blood loss, reduced postoperative pain, shorter hospital stays, fewer postoperative complications within 30 days, and lower mortality rates compared to open surgical procedures [43].

The fundamental principles of adrenal surgery in the case of PCC include early identification and ligation of the adrenal vein, minimal manipulation of the tumor to prevent rupture or the release of catecholamines, which can cause fluctuations in blood pressure [43].

Laparoscopic adrenalectomy is recommended for the treatment of many patients with PCC. While laparoscopic adrenalectomy is typically recommended for PCCs up to 6 cm, open adrenalectomy is recommended for ensuring complete tumor resection, preventing tumor rupture, and minimizing local recurrence in tumors greater than 6 cm. Open surgery is recommended for PGLs, as these tumors have a higher risk of malignancy and are often located in anatomically challenging areas for laparoscopic resection. However, laparoscopic surgery may be performed for small, non-invasive PGLs in an appropriate location, provided that resection of adjacent organs is not required [43].

Larger tumors are associated with a higher risk of both metastasis and tumor rupture. The rupture of the primary PCC during surgical resection can lead to the spread of tumor cells into the abdominal cavity, causing peritoneal and retroperitoneal dissemination. This can result in the development of peritoneal carcinomatosis and metastatic disease, which, if not properly treated, can potentially be fatal. Therefore, complete removal of the tumor without rupture is crucial for ensuring a favorable prognosis for the patient. Moreover, in the case of tumor rupture, patients should be closely monitored, as recurrence of the disease may occur even after prolonged remission. Preoperative determination of the type of germline mutation in PPGL is of significant importance for selecting the appropriate surgical strategy and the extent of adrenalectomy, which can greatly influence the further course of treatment and the patient's prognosis [43].

Open adrenalectomy may be preferred for patients with germline mutations in SDHB, TMEM127, or FH, as the risk of extra-adrenal disease, metastasis, or recurrence is higher than in patients with germline mutations in NF1, RET, or VHL. Open surgery is preferred in patients with multifocal lesions where laparoscopic approach is not feasible. In rare cases, en bloc resection may require removal of surrounding organs. In such cases, open surgery should be favored. In metastatic diseases, metastases primarily occur in lymph nodes, so locoregional lymph node dissection should be performed together with the primary tumor

during laparotomy in patients where lymph node metastases are detected on preoperative imaging or during intraoperative assessment, or in patients with a high risk of lymph node metastasis, such as those with SDHB germline mutation. The surgery may be radical in cases of metastasis to regional lymph nodes. Although PGLs are less common than PCCs, they are more likely to be malignant. Malignant PGLs often have a dense fibrous capsule and adhere to surrounding vascular structures, which can complicate complete resection. Preoperative preparation should be done in case vascular reconstructions with en bloc resection are required. Many primary PGLs are often clinically indistinguishable from metastases to the aortocaval lymph nodes, and in such cases, regional lymph node dissection should be performer [43].

Partial adrenalectomy or adrenal-sparing surgery may be performed in some selected patients with PCC to preserve adrenal cortex function and avoid lifelong steroid therapy, which negatively impacts quality of life. Adrenal-sparing surgery is preferred in patients at high risk for bilateral disease and with a low likelihood of malignant tumors, such as those with MEN2 or VHL syndrome. Although the exact amount of residual adrenal tissue is unknown, this approach has been shown to prevent postoperative adrenal insufficiency in up to 90% of patients [39,43].

3.6. Intraoperative Management

Esmolol is the most commonly used agent for intraoperative hypertension. Intravenous magnesium sulfate may be used in cases of hypertension resistant to treatment. During surgery, an increase in blood pressure and arrhythmias may be observed when manipulating the tumor. In such cases, manipulation is interrupted until blood pressure is reduced. If necessary, the anesthesiologist can administer medications to lower blood pressure. After tumor resection, hypotension may occur. In such cases, isotonic fluid (0.9% NaCl) is administered intravenously. If needed, a bolus or infusion of ephedrine or phenylephrine can be given [43].

3.7. Postoperative Care

Serious postoperative complications include hypotension and rebound hypoglycemia, and patients should remain under close observation for 24–48 hours. Blood pressure, heart rate, urine output, and blood glucose levels should be closely monitored. Acute postoperative hypotension is generally associated with a sudden drop in circulating catecholamines and the expansion of the intravascular space due to the residual effect of α -blockade. Intravenous fluid resuscitation is required. If necessary, vasopressor medications (ephedrine, phenylephrine, norepinephrine) can be administered. Reactive hypoglycemia may occur after PPGL resections, though it is relatively uncommon. High levels of catecholamines inhibit α and β cells in the pancreas. Postoperatively, rebound hyperinsulinemia may develop. Associated hypoglycemia usually occurs within the first four hours after surgery. Blood glucose levels should be checked every six hours. Intravenous 5% dextrose should be administered until the patient can tolerate oral intake, and insulin requirements should be adjusted postoperatively, especially in patients with diabetes [43].

3.8. Postoperative Outcomes

PPGL increases cardiovascular morbidity and mortality. When the causes of death were evaluated in autopsy studies of patients with undiagnosed and untreated PCCs, it was found that 71% of these patients died from cardiovascular causes, such as myocardial infarction, hypertensive heart failure, stroke, or hemodynamic crises during unrelated interventions [43].

In the study by Stolk et al. [49] it was found that in patients with PCCs, the risk of cardiovascular complications, such as myocardial infarction, stroke, or angina, is 14 times higher compared to patients with primary hypertension within five years prior to diagnosis. This is not related to differences in blood pressure or other cardiovascular risk factors, and the most likely explanation for this phenomenon is prolonged exposure to the toxic effects of tumor-derived catecholamines [43].

In another retrospective study, 64% of patients with benign PCCs showed a significant reduction in blood pressure after surgery. Only one-third of patients achieved normotension without medication. In the follow-up of these patients, the expected lifespan was similar for those who did not develop metastases, compared to the matched population, but lower for those who developed metastatic disease. Therefore, lifelong monitoring of these patients is crucial in the context of metastatic disease. In the series by Beninato et al., diabetes was detected in 23% of PCC patients, with 93% showing improvement in diabetes after surgery, and 78.6% achieving complete resolution [43,50].

3.9. Head and Neck PGLs

Head and neck PGLs are generally non-functional and are named according to the anatomical area from which they originate, such as carotid body PGL, glossopharyngeal nerve PGL (middle ear), vagus nerve PGL, and laryngeal PGL. Carotid body PGLs make up more than half of head and neck PGLs. Less than 5% of all head and neck PGLs metastasize, with a lower metastasis rate seen in carotid artery PGLs. Hereditary head and neck PGLs may be multiple and occur in association with sympathetic PGLs. Germline mutations are less than 20% in patients with sporadic tumors and significantly higher in patients with a family history. The most commonly observed mutations are in the SDHx genes. PGLs associated with SDHB mutations have a high risk of metastasis. Traditionally, surgical resection has been the first-line treatment for most carotid body PGLs, but recent evidence showing that many tumors have relatively low malignancy rates has increased interest in non-surgical treatment or observation. The morbidity associated with surgical resection can be avoided by actively monitoring patients with indolent disease, taking into account the risk of metastasis, tumor biology, growth rate, tumor size, patient age, and mutation status [43].

Carotid body PGLs are often associated with germline mutations. SDHx mutations are the most common and are linked to paraganglioma syndromes 1 through 4 (corresponding to mutations in SDHD, SDHAF2, SDHC, and SDHB). While SDHB mutations lead to more aggressive disease and higher metastasis rates than SDHD mutations, SDHD mutations are more commonly associated with head and neck PGLs, which have higher incidence rates, while PCCs are less common. Ellis et al. [51] studies have shown that PGLs of the carotid body with SDHB mutations are associated with poorer disease-free survival after resection, despite early intervention. In these patients, a more aggressive surgical approach is required. However, in cases of carotid body PGL without SDHB mutations, it has been reported that if the lesion is asymptomatic, its diameter is smaller than 2 cm, and it is not biochemically hormonally active, observation may be considered as an option [43].

In the case of carotid body PGL, the risk of stroke and cranial nerve damage is significantly increased because the tumor is closely associated with surrounding vessels, making resection more challenging (Shamblin classification: type 3 > type 2 > type 1). The overall stroke rate after carotid body PGL resection is 3.5%, while the rate of cranial nerve damage persisting longer than 30 days is 11.5%. The rate of neck hematomas requiring re-exploration is 5.2%, and preoperative embolization does not reduce the rate of hematomas requiring re-exploration. In patients with multifocal disease, including lesions in the head and neck region as well as outside the neck, extra-cervical lesions should be resected prior to addressing the carotid body PGL. PGLs located outside the head and neck region are more likely to exhibit hormonal activity [43].

For cervical and mediastinal PGLs, a transcervical approach is typically used, although it is rarely combined with transmandibular, transclavicular, or infratemporal approaches. Carotid body PGLs involving the ICA have a higher incidence of complications. In the case of erroneous PGLs, a cervical or posterior foramen approach is recommended. If significant intraspinal extension is present, a two-stage surgery may be required. Resection of cervical PGLs varies in complexity. Tympanic PGLs are typically excised via a low-morbidity transcanal microscopic/endoscopic approach. Tympanosutural PGLs involve transclavicular, transcanal, and sublabyrinthine techniques, sometimes requiring middle ear removal, all of which have low morbidity concerning facial and lower cranial nerves. Cervical PGLs can weaken the ICA and lower cranial nerves and extend into the IDS. The infratemporal approach in these cases poses significant technical challenges (protection of the ICA with a stent or its occlusion may be necessary for total resection) and functional morbidity, especially if the IDS or lower facial and hypoglossal nerves are involved (> 30%). There is no consensus on systematic facial nerve rerouting. Partial resection may be a reasonable option for tumors extending into the external auditory canal that cause recurrent hemorrhage in elderly patients [39].

3.10. Management of PPGL in Pregnancy

The adverse effects of PPGL on both the mother and the fetus are primarily caused by significantly elevated levels of catecholamines [52,53].

Effective management of hypertension during pregnancy is also essential to maintain proper uteroplacental circulation, thereby reducing the risk of intrauterine growth restriction (IUGR) or fetal death [54]. Administration of α-adrenergic receptor blockers has been associated with improved outcomes. The two most commonly used α-adrenergic receptor blockers are phenoxybenzamine (a non-selective antagonist) and doxazosin (a selective α-1 receptor antagonist), with neither demonstrating a clear superiority over the other in achieving normotension during pregnancy. Phenoxybenzamine crosses the placenta and is associated with hypotension and respiratory depression in newborns. Although doxazosin also crosses the placenta, no adverse

effects have been reported in newborns of mothers treated with this drug. Both agents are considered safe for use during breastfeeding [55].

The optimal timing for surgical resection of PPGL diagnosed during pregnancy remains a subject of debate. Surgery is generally recommended when PPGL is diagnosed before 24 weeks of pregnancy, while in cases diagnosed during the third trimester, resection is often delayed until after delivery. The second trimester is considered the safest period for surgery due to a lower risk of spontaneous miscarriage compared to the first trimester. In the third trimester, anatomical changes make laparoscopic adrenalectomy more challenging. Pregnancy has a two-fold higher likelihood of reaching full term when tumors are removed preterm (81%) compared to post-term (41%), and fetal distress, as indicated by Apgar scores, is more common when the tumor is not removed before delivery. Overall, it is accepted that the timing of surgical resection should be determined individually, considering the specific circumstances of each case. The preferred surgical method is laparoscopic tumor removal, with a complication rate of less than 8%, making it a safe treatment option for PPGL during pregnancy [55].

An increasing body of evidence supports the feasibility of a successful vaginal delivery in selected cases of PPGL, provided that adequate α-adrenergic receptor blockade is achieved. In such cases, elective epidural anesthesia and passive second-stage labor are recommended to minimize the risk of tumor stimulation due to increased intra-abdominal pressure during maternal pushing. However, cesarean section remains the preferred method of delivery for women with larger tumors, particularly those located in the abdominal or pelvic cavity, as well as in cases with significantly elevated catecholamine levels. The timing of delivery is typically determined based on fetal well-being and maternal blood pressure control. Indications for early delivery include IUGR, decreased fetal movement, fetal heart rate deceleration, and/or unstable maternal blood pressure [55].

3.11. Systemic Chemotherapy

Metastatic disease, if not amenable to complete surgical resection, is considered incurable, with a risk of metastasis in 15-17% of cases. Metastatic PPGL is defined as the presence of metastatic lesions in lymph nodes, bones, lungs, or liver (WHO) [56]. Treatment options for systemic therapy are limited, but they can provide symptom relief and disease control. However, due to the relatively indolent nature of PPGL, these therapies are typically reserved for patients with significant disease progression or severe symptoms caused by hormone secretion or mass effects [2,12,39].

3.12. Systemic Chemotherapy Regimens

Systemic chemotherapy regimens can be used to control tumor growth in rapidly progressing diseases. Cyclophosphamide, vincristine, and dacarbazine are standard treatment protocols for these patients. Information about signaling pathways and mutations in PPGL can aid in targeted treatment. Targeted therapeutic agents, such as TKIs associated with these signaling pathways, may be considered in therapy [39,43].

A systematic review of four retrospective series involving 50 patients showed an objective tumor response rate of 41% (4% complete responses and 37% partial responses) and a biochemical response rate of 54% (14% complete responses) [57]. Two of these studies reported a median response duration of 20 and 40 months, respectively. In the largest single-center experience with chemotherapy (54 patients), 33% of patients achieved a response, defined as improvement in blood pressure control and/or tumor size reduction. The overall survival (OS) was 6.4 years for patients who responded to treatment compared to 3.7 years for those who did not, with this difference being statistically significant in multivariate analysis [58].

The most common toxicities include myelosuppression, peripheral neuropathy, and gastrointestinal toxicity, which can sometimes be severe but are generally transient and manageable. A retrospective study of 15 patients treated with temozolomide (150-200 mg/m²/day on days 1-5 every 28 days), 8 of whom had previously received chemotherapy, documented 5 partial responses (33%) that occurred only in patients with SDHB mutations [39,59].

3.13. Inhibitors of Tyrosine Kinase

A number of TKIs are being studied due to the crucial role that angiogenesis regulation plays in PPGL. The Phase II SNIPP trial assessed sunitinib in 25 patients with progressive PPGL [60]. The overall response rate was low (13%) in the entire unselected population, although all three partial responses occurred in patients with germline mutations in SDHA, SDHB, and RET (with the latter patient continuing treatment 7 years later). The disease control rate (DCR) was 83%, meeting the primary endpoint of the study, and the median

progression-free survival (PFS) was 13.4 months. The most common severe adverse events were fatigue and thrombocytopenia (16% each), with three patients discontinuing treatment due to cardiovascular events. Sunitinib is currently being assessed in the first randomized placebo-controlled trial ever conducted in PPGL, the FIRSTMAPPP trial. A Phase II trial with pazopanib was prematurely terminated due to poor patient recruitment. One of six evaluated patients achieved a partial response (17%), and the median PFS and OS were 6.5 and 14.8 months, respectively [61]. Similarly, preliminary data from a Phase II trial with axitinib showed an objective response in three of nine treated patients (33%) and some degree of tumor reduction that did not qualify as partial response in five additional patients, which was associated with a biochemical response [62]. Other TKIs (cabozantinib, lenvatinib, etc.) are currently being evaluated in clinical trials [39].

3.14. Radiotherapy and Radiopharmaceuticals

The largest experience with radiotherapy in PGL comes from the treatment of neck PGLs, as radiotherapy provides a non-invasive therapeutic option that is suitable for high surgical risk areas or when patients are not candidates for surgery (e.g., those with carotid artery or intracranial involvement). Conventional radiotherapy yielded moderate responses (20-30%), which were surpassed by single-dose stereotactic radiotherapy (12-15 Gy) and later by stereotactic ablative radiotherapy (SABR) with doses of 20–25 Gy in 3-5 fractions, leading to a tumor control rate of 90-100% and symptomatic improvement in 80% of patients [39].

Before PRRT, functional imaging studies with 123I-MIBG and/or radiolabeled SST analogs should be performed to assess tumor affinity for the radiotracer and select the most appropriate radiopharmaceutical for each case [39]. Currently, 131I-MIBG therapy is the most well-researched treatment for metastatic PPGL and is recommended as first-line therapy for patients with positive 123I-MIBG scans and slowly growing metastatic disease. In a multicenter Phase II study, partial radiological response and disease stabilization were achieved in 92% of patients treated with high-specific activity 131I-MIBG (AZEDRA, Progenics Pharmaceuticals Inc). Biochemical and clinical responses can be achieved using advanced somatostatin analogs, such as 90Y-DOTATATE or 177Lu-DOTATATE, in metastases with positive somatostatin receptors in advanced PPGLs [43].

Radiotherapy, radiofrequency ablation (RFA), radiosurgery (gamma knife/cyberknife), and cementoplasty are palliative treatment options for painful bone metastases. Anti-resorptive therapy, such as bisphosphonates or denosumab, should be considered for bone metastases. In cases of epidural spinal cord compression, patients with spinal instability may benefit from a combination of spinal surgery and external radiotherapy. For hormonally active metastatic patients, cardiovascular stability should be established using α-adrenergic blockade, and β-blockers should be added as needed. Surgery should be considered in cases of urinary tract obstruction [43].

3.15. Direct Future Research Directions and Clinical Practice

Future research directions closely tied to clinical practice will require large-scale inter-institutional collaboration to obtain solid, useful, and easily translatable results for patient care. Promising applications include the use of PARP inhibitors in combination with temozolomide, alpha-mimetic bone-targeting agents (223RaCl2; Xofigo®), various approaches to somatostatin receptor-targeted radiotherapy, immunotherapy, and radioimmunotherapy. These strategies are on the horizon, and there is considerable potential for them to improve treatment outcomes. In the near future, treatment options will also benefit from new schedules, timing paradigms, potential synergistic combinations, advanced bioinformatics tools, and artificial intelligence (AI). These technologies will assist in refining therapeutic approaches and optimizing treatment regimens. Additionally, the exploration of new targets, biomarkers, oncometabolites, long non-coding RNAs (lincRNA), and signaling pathways is essential for improving the identification, understanding of tumor pathogenesis, and localization of PPGLs. These research avenues could lead to more personalized and effective treatment strategies [12,63].

3.16. Initial Postoperative Assessment

Early postoperative monitoring focuses on confirming tumor removal and establishing a baseline for long-term surveillance. The first post-surgical check-up is typically scheduled within 2-6 weeks after surgery. At this visit, patients undergo a thorough clinical evaluation (including blood pressure and symptom review) and biochemical testing to ensure that catecholamine levels have normalized [39]. The biochemical tests of choice are measurements of plasma free metanephrines (or alternatively 24-hour urinary fractionated metanephrines), which

are the most sensitive markers for PPGLs [6]. Levels of normetanephrine and metanephrine – metabolites of norepinephrine and epinephrine – should fall to normal after complete resection of a secreting tumor. If the tumor had produced dopamine or was of a noradrenergic phenotype, 3-methoxytyramine should also be measured, as elevated 3-methoxytyramine can indicate residual or recurrent disease in such cases. In practice, an early postoperative normalization of these metabolites strongly suggests biochemical cure, whereas any persistent elevation may raise concern for incomplete resection or metastasis [39].

In addition to labs, selective imaging is considered in the early postoperative period. Routine immediate imaging is not necessary for every patient, but an imaging study around 3 months after surgery is recommended for certain scenarios. For example, if a patient's biochemical markers remain abnormal after surgery, or if the original tumor was biochemically silent (non-secretory) making lab monitoring less reliable, an early postoperative MRI or CT scan (~3 months post-op) can help detect any residual tumor or new lesions. Imaging at 3 months is also advised if no proper preoperative imaging or biochemical workup was done, to establish a new baseline [39].

3.17. Long-Term Follow-Up: Frequency and Duration

After the immediate postoperative period, patients enter a long-term surveillance phase. Regular follow-up is mandatory for all PPGL patients given the tumor's unpredictable behavior. The appropriate frequency of follow-up visits may vary with time and risk, but annual evaluations are generally recommended as a standard for asymptomatic patients. In clinical practice, most centers advise patients to return yearly for assessment of symptoms, blood pressure, and biochemical testing. More frequent monitoring (e.g., every 6 months) may be employed in the first couple of years or in higher-risk cases, since data indicate the majority of recurrences tend to occur within the initial years post-surgery. A recent multicentre study found the highest incidence of new recurrence was in the first 0-2 years after resection [64].

The duration of follow-up has been a subject of evolving recommendations. Earlier guidelines such as the Endocrine Society (2014) advised lifelong follow-up for all patients due to the possibility of late recurrence. The European Society of Endocrinology's guideline introduced a risk-adapted approach, suggesting at least 10 years of biochemical follow-up for low-risk patients and lifelong surveillance for high-risk patients (those who are young, had larger tumors, genetic mutations, or PGLs). In practice, a minimum of 10 years of annual follow-up is recommended for every patient with a resected PPGL [65]. After 10 years, some truly low-risk patients (e.g., older individuals with a small sporadic adrenal PCC) might be considered for de-escalation of surveillance. However, emerging evidence supports extending follow-up further: a significant proportion of "sporadic" cases still develop late recurrences beyond the 10-year mark. In one large study of over 1,100 patients, about 14.7% of patients with sporadic PPGL had recurrences, and notably nearly one-third of those recurrences were diagnosed over 10 years after the initial surgery [66]. Another series reported cases of recurrence occurring as late as 15-48 years post-surgery [65]. Given these observations, many experts now advocate lifelong follow-up even for apparently sporadic or benign cases, as the safest course. In summary, all patients should be monitored for at least a decade, and indefinite (lifelong) follow-up is strongly recommended for higher-risk individuals - and indeed is advised for most patients by many centers - in order to catch late recurrences that do rarely occur [64,67].

3.18. Surveillance Modalities: Biochemical Markers and Imaging

The two pillars of postoperative surveillance for PPGL are biochemical monitoring and imaging studies. Biochemical tests serve as a sensitive way to screen for recurrent disease. Plasma-free metanephrines (or 24-hour urinary fractionated metanephrines) are considered the gold-standard biochemical marker for follow-up [6]. These metabolites (normetanephrine and metanephrine) remain elevated if any catecholamine-producing tumor tissue persists or recurs, making them highly useful for detecting occult recurrences. In practice, patients are usually instructed to have annual blood or urine tests for metanephrines as part of their follow-up [64]. In addition, if the original tumor secreted dopamine or was an SDHB-related tumor (often producing dopamine or methoxytyramine), plasma 3-methoxytyramine should also be measured regularly. An elevated 3-methoxytyramine can be an early sign of recurrence in tumors with a dopaminergic phenotype [65]. Some centers also monitor CgA levels, a general neuroendocrine marker, especially if the tumor was biochemically silent or if metanephrine levels are normal despite suspicion of recurrence. However, metanephrines are the primary and most specific test; CgA is only used as a supplementary marker when other tests are negative but clinical suspicion remains. Overall, yearly biochemical screening with appropriate markers (tailored to the tumor's secretory profile) is crucial for early detection of recurrent PPGL [39].

Imaging surveillance is the complementary modality to biochemical follow-up. Imaging is not required at every visit for all patients, but it plays a key role in certain intervals and circumstances. Current expert recommendations suggest periodic imaging every 1-3 years for asymptomatic patients, with the frequency adjusted based on risk factors and biochemical results. For example, in a patient with negative biochemical tests and no symptoms (especially if their tumor was secretory), routine imaging might be spaced to every 2-3 years. On the other hand, any abnormal lab results or new clinical symptom (e.g., return of hypertension, headaches, sweating spells) should prompt immediate imaging regardless of schedule. The preferred imaging modality for surveillance is MRI, particularly for younger patients and those with hereditary syndromes. MRI avoids radiation exposure and can cover the abdomen (for adrenal or abdominal PGLs) or neck and chest (for head/neck or thoracic PGLs) without cumulative dose concerns [39]. CT is an alternative when MRI is contraindicated or unavailable, but clinicians aim to minimize repeated CT scans in patients who require lifelong follow-up [6]. In patients with known metastatic disease or very high-risk features, functional imaging may be incorporated: for instance, 123I-MIBG scintigraphy is advised by some experts if the risk of metastasis or recurrence is high. Similarly, 18F-FDG positron emission tomography (PET)/CT or other nuclear medicine scans are generally reserved for cases where metastatic disease is established or strongly suspected, rather than routine follow-up of a patient in remission [39].

3.19. Adverse Prognostic Factors

The presence of metastatic disease at diagnosis is the strongest predictor of poor outcome, associated with drastically shorter survival than localized cases [68]. Large primary tumor size is another key risk factor: for example, tumors over about 5 cm are more likely to metastasize or recur [69]. Extra-adrenal location and local invasion (e.g., adjacent organ or lymph node involvement) also correlate with higher malignant potential and worse survival [70]. Additionally, characteristics such as older age and male sex have been linked to more aggressive disease, [68] echoing observations that these traits often accompany rapidly progressive disease [71].

Genetic background plays a major role in PPGL prognosis. Up to 30-40% of patients have germline mutations, and certain mutations confer particularly high metastatic risk. Notably, a SDHB mutation is associated with an elevated likelihood of metastasis (often >50% lifetime risk), whereas PPGLs due to mutations in RET, VHL or NF1 have much lower malignant potential [70]. Identifying a patient's genotype is therefore critical for risk stratification. Some histological scoring systems (e.g., PASS) and immunohistochemical markers (like the Ki-67 index) have been proposed as predictors, but none are fully reliable [69,72].

3.20. Early Detection and Improved Outcomes

Because advanced PPGL can cause life-threatening catecholamine crises and metastasis, early diagnosis is crucial for improving outcomes. Timely biochemical screening and imaging work-up lead to prompt tumor localization and curative surgery before significant progression; modern functional scans can further aid in detecting occult lesions at an early stage. In hereditary cases, proactive surveillance has proven beneficial. For example, regular screening of SDHB mutation carriers has been shown to detect tumors earlier and dramatically reduce metastatic risk and mortality, [73] supporting periodic surveillance in such high-risk individuals. Similarly, integrating germline genetic testing into routine care helps identify at-risk patients and can improve outcomes - one study reported better 5-year survival with fewer metastases in mutation carriers managed with tailored follow-up. Overall, combining these diagnostic approaches has measurably improved outcomes [74].

4. Conclusions

PPGLs are among the diagnoses that pose a clinical challenge. The relative rarity of occurrence and the lack of definitive symptoms necessitate in-depth diagnostics in every case of secondary hypertension. More and more data indicate a genetic basis for the occurrence of PPGLs. The diagnostic path includes a number of laboratory and imaging tests. Medical progress in the field of diagnostics allows for an increasingly faster diagnosis, but the overall clinical picture is still a challenge. It is important to carefully evaluate the diagnosis and treatment in a multidisciplinary team that should include an internist, hypertensiologist, radiologist, and surgeon. In selected cases, consultation with pediatricians and gynecologists should also be included. The scope of selected pharmacological and surgical therapy should be adjusted to each patient individually. This is to protect against adverse effects and ensure a favorable prognosis for the patient. Medical progress in diagnostics, treatment and surgical methods allows for therapy tailored to each patient. The following years bring more and more publications on the pathogenesis of PPGLs. However, it should be emphasized that further research is necessary, which will increase the chances of faster diagnosis and improve the patient's prognosis.

Disclosure
Author's Contribution:
Conceptualization: KR
Methodology: DŻ
Software: KR, MKo, DŻ
Check: KR, DŻ
Formal analysis: AZ, KZ, SK
Investigation: KR, AJ, SK, MKo
Resources: MKr, KZ, AZ
Data curation: MKo, MKr, AJ
Writing - rough preparation: KR, MKo, AZ, AJ, SK, KZ, MKr
Writing - review and editing: KR, DŻ
Visualization: AZ, AJ
Supervision: KR, DŻ
Project administration: KR, DŻ

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external funding.
Institutional Review Board Statement: Not applicable.
Informed Consent Statement: Not applicable.
Data Availability Statement: Not applicable.
Acknowledgments: Not applicable.
Conflict of Interest Statement: The authors declare no conflict of interest.

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