ADRENAL AND EXTRA-ADRENAL PARAGANGLIOMA

IN CHILDREN AND ADOLESCENTS

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EUROPEAN STANDARD CLINICAL PRACTICE

RECOMMENDATIONS

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PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS IN CHILDREN AND ADOLESCENTS

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1. Background and rationale

1.1 Summary

Paediatric very rare tumours (VRT) constitute an extremely heterogeneous group of neoplasms. Some of them are typical for paediatric age, while others more commonly arise during adulthood and only rarely develop in children. Using the definition *any solid malignancy or tumour of uncertain clinical behaviour characterized by an annual incidence < 2/million children <18 years of age*, the European Cooperative Study Group for Paediatric Rare Tumours (EXPeRT) has initially identified a number of paediatric VRT (1). Due to the low number of patients, it is very difficult – or even impossible – to conduct prospective clinical trials on them, and this makes it demanding to develop evidence-based treatment guidelines. Consequently, the treatment of patients with VRT is often individualized.

Background: Paediatric adrenal (formerly termed pheochromocytomas) and extra-adrenal paragangliomas (PGLs) are rare neuroendocrine tumours that develop from chromaffin cells of the adrenal medulla and from extra-adrenal paraganglia, respectively. Even more frequently than their adult counterparts, paediatric PGLs have a strong hereditary component, with up to 80% of cases linked to germline pathogenic variants. predominantly in genes affecting the pseudohypoxic (cluster 1) pathway. In contrast, hereditary cluster 2 (kinase signalling) variants are rare in children. Given this genetic predisposition, lifelong surveillance is often required, and family screening plays a crucial role in early detection.

PGLs can present with a variety of clinical symptoms, most commonly hypertension, tachycardia, headaches, excessive sweating, and anxiety-like episodes, which result from

excess catecholamine secretion. However, due to the episodic and sometimes non-specific nature of symptoms, timely recognition remains a challenge but requires biochemical confirmation with plasma-free or urinary metanephrines, cross sectional imaging and occasionally functional imaging to localize the tumours.

Primary tumour resection remains the gold standard for curative treatment, with minimally invasive adrenalectomy preferred for localized tumours, while open surgery is required for larger or extra-adrenal paragangliomas. Preoperative medical optimization, particularly with alpha-adrenergic blockade, is critical to prevent perioperative complications. In cases of unresectable or metastatic disease, treatment options include observation, focal therapies of distant sites (surgery, radiotherapy, thermal therapy), targeted therapies, and [131I]I-MIBG therapy. The use of somatostatin receptor-directed peptide receptor radionuclide therapy (PRRT), although supported by emerging data including recent paediatric studies, should be considered primarily within clinical protocols or following careful multidisciplinary team review and critical appraisal of the most recent evidence. Systemic therapies tailored to the molecular profile of the tumour may also be employed in selected cases.

Objective: To establish internationally harmonized consensus recommendations for the diagnosis and treatment of children and adolescents with pheochromocytomas and paragangliomas ("Standard of care recommendations for children with VRT").

1.2 Background

Pheochromocytomas and paragangliomas are rare neuroendocrine tumours that develop from chromaffin cells of the adrenal medulla and from extra-adrenal paraganglia, respectively. (1, 2) In the 2022 World Health Organization (WHO) classification, pheochromocytoma is designated as (intra-) adrenal paraganglioma (PGL), within the unified PGL family. (3) PGLs are further divided by autonomic lineage into sympathetic PGLs including adrenal PGLs and extra-adrenal sympathetic chain tumour; typically catecholamine producing) and parasympathetic PGLs (predominantly head-and-neck; usually non-secretory).

While the majority of PGLs present in adulthood, approximately 8–13% of cases are diagnosed before the age of 18. (4, 5) However, considering their slow-growing nature and the frequent delay in diagnosis, the true prevalence of PGLs originating in childhood and adolescence may be underestimated, and could potentially exceed 20%.

Paediatric PGLs exhibit distinct clinical and molecular characteristics compared to adult-onset cases. A striking feature of paediatric disease is its strong hereditary basis, with germline pathogenic variants detected in up to 80% of cases, in contrast to 40–50% in adult patients. (6-9) The predominant genetic alterations observed in paediatric cases fall within the pseudohypoxia-driven molecular cluster, particularly affecting genes such as von Hippel-Lindau (*VHL*) and any of the succinate dehydrogenase subunit genes (*SDHx*). (8, 9) These genetic alterations are associated with a high risk of multifocal disease, recurrence, and metastatic progression (particularly in *SDHB* mutated tumours), necessitating a genotype-driven approach to diagnosis, treatment, and long-term surveillance. (10, 11)

The estimated annual incidence of paediatric PGLs is 0.5–2 cases per million children, with a median age at diagnosis ranging from 11 to 15 years. (4-6, 12-14) While a slight male predominance has been described in some studies, others report an equal gender distribution. Notably, PGLs are significantly more prevalent among children with secondary hypertension than among adults, accounting for 1–2% of cases in paediatric populations compared to only 0.2% in adults. (13, 15) Although the presence of sustained or paroxysmal hypertension should prompt clinicians to consider PGL as a potential underlying cause, its absence does not exclude the diagnosis. Many children with catecholamine-producing tumours may present without hypertension, and clinicians should remain alert to other signs of catecholamine excess, such as pallor, excessive sweating, palpitations, and headaches. (5, 14, 16-18)

The heritability of PGLs is among the highest of all endocrine tumours, with over 20 germline susceptibility genes identified to date. These inherited genetic alterations are primarily grouped into two molecular clusters: pseudohypoxic (*VHL*, *SDHx*, *EPAS1*, *FH*), and kinase signaling (*RET*, *NF1*, *TMEM127*, *MAX*, *HRAS*). (7, 19, 20) A third group, known as the Wnt-altered cluster (*CSDE1*, *MAML3*), involves somatic gene alterations found within tumour tissue and does not contribute to hereditary transmission. (19, 21) Paediatric PGLs overwhelmingly belong to the pseudohypoxic group, whereas adult cases demonstrate a more balanced distribution across all three molecular clusters. (7, 8, 20-22) This distinction is also reflected in biochemical profiles; paediatric PGLs are predominantly noradrenergic, characterized by high levels of norepinephrine and the absence of epinephrine due to deficient expression of phenylethanolamine N-methyltransferase (PNMT) in tumours driven by *VHL* and *SDHx* pathogenic variants. (23, 24)

The clinical presentation of paediatric PGLs is largely driven by catecholamine excess. Hypertension is the most common symptom, present in 70–90% of cases, often accompanied by palpitations, excessive sweating, headaches, nausea, anxiety, and exercise-induced vomiting. (4, 9, 14, 25, 26) Some children present with symptoms related to tumour mass effect, particularly in cases of extra-adrenal paragangliomas, which may cause abdominal pain or neurological deficits. (27) Noteworthy, some tumours – particularly those associated with cluster 1 pathogenic variants such as *SDHx* – may remain clinically silent if detected at an early stage or small size, while truly non-functional tumours due to absent tyrosine hydroxylase expression are exceptionally rare. (28)

Despite these hallmark features, paediatric PGLs are frequently associated with delayed diagnosis. (29) Symptoms can be episodic, nonspecific, or misattributed to anxiety disorders, hyperactivity, or other conditions, leading to a median diagnostic delay of 6–7 years. (30) This underscores the need for increased awareness and systematic screening in high-risk populations, particularly among children with a known genetic predisposition. (10, 20, 31)

Paediatric PGLs also differ significantly from adult-onset disease in anatomical distribution, recurrence risk, and prognosis. (6, 14) Children more frequently present with extra-adrenal tumours, with up to 40% of paediatric cases arising as paragangliomas compared to 20% in adults. (6, 14) Multifocal and bilateral disease is also more common in paediatric cases. (6, 14) Furthermore, paediatric PGLs demonstrate higher recurrence and metastatic potential, with up to 50% of patients experiencing disease recurrence. In comparison, recurrence rates in adults are approximately 14% in sporadic cases, 47% in hereditary cluster 1 PGLs, and 15% in hereditary cluster 2 PGLs. (6, 14)

The overall survival rate for paediatric PGLs is favourable, ranging from 98 to 100% at five years. (9) However, disease-free survival is significantly lower, at approximately 54%, due to high rates of recurrence and the development of new lesions in the context of hereditary disease. (6, 9) Metastatic disease is present in 10–20% of paediatric cases at initial diagnosis and is associated with increased long-term morbidity and mortality. (6, 14, 32) While complete surgical resection remains the primary curative treatment, the extent of resection is a critical prognostic factor, with incomplete tumour resection being the strongest predictor of poor disease-free survival. (8) Emerging targeted therapies, such as HIF2α inhibitors for pseudohypoxic tumours, offer promising avenues for improving long-term outcomes in high-risk patients.

An international consensus statement on the management of paediatric PGL has recently been published, offering comprehensive expert recommendations across the diagnostic and therapeutic spectrum, based on a Delphi process. (11)

Here, we present European Standard Clinical Practice (ESCP) recommendations for the diagnosis, treatment, and long-term management of paediatric PGL established by the European Cooperative Study Group for Paediatric Rate Tumours (EXPeRT). While closely aligned with the global consensus, this ESCP aims to provide a concise, clinically structured, and implementation-focused framework tailored to paediatric oncology practice in Europe and aiming to standardize care across European centres.

2. Methodology

According to the Consensus Conference Standard Operating Procedure methodology, the levels of evidence can be classified from Level I to V and the grades of recommendation A to E (*Table 1) (54)*.

Table 1. Levels of evidence and grades of recommendation (adapted from the Infectious Disease Society of America-United States Public Health Service Grading System)

Levels of Evidence	
I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of Recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional

D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

EXPeRT members recognized that due to the rarity of this tumour, no evidence of Level I to II exists for this age group. Therefore, recommendations for VRTs are developed based on the evidence collected from some published prospective studies (Level III), but more frequently retrospective series (Level IV), case reports (Level V) and personal expertise (Level V). In addition, the "strength" of recommendations will be categorized by additional grading (Grade A to E).

To identify tumours that need shared recommendations, EXPeRT members designed the following procedure:

- Identification of the tumour of interest on the basis of its relevance, and previous EXPeRT experience, (i.e., data analysis and publication). Tumours should be classified as VRT (i.e. < 2/100.000/inhabitants/year), not already analysed in previous Expo-r-Net project, as pulmonary pneumoblastoma, pancreatoblastoma, thymic tumours, rare sarcomas, not included in specific international protocols and frequent enough to be of interest[1].
- Designation of two main coordinators for each VRT based on their experience (data analysis, publications, personal experience).

Coordinators must:

- Analyse the medical literature and select the relevant papers.
- Propose a series of recommendations in the form of a first draft of recommendations.
- Identify the main diagnostic and therapeutic problems for the designated VRT. The first drafts will be shared and discussed, along with the relevant publications, into a selected expert group of EXpERT members and annotated.
- A mature version of recommendations will be produced, considering proposals from the group of selected EXPeRT members.
- The annotated draft will be then proposed to external experts identified by the coordinators based on a recognized experience on the tumour (paediatrician, medical oncologist, radiation oncologist, surgeon…).

- The final version will be validated by the whole group. In case of remaining disagreements, a vote will be done, during a physical consensus meeting, to agree on in a final consensus.
- Validated version will be submitted for publication in an open-source peer review journal.

The final document including recommendations will be available on EXPeRT and SIOPe websites.

NB: These guidelines may change over time according to new data available. Local clinicians remain responsible for the care of their patients. The EXPeRT members are not responsible for results or complications related to their use. If necessary, medical discussions are possible with EXPeRT members via the ERN CPMS website: CPMS 2.0

3. Patient group

3.1 Diagnostic criteria

Paediatric PGLs present with a wide spectrum of clinical manifestations, primarily driven by catecholamine excess. The most common symptoms include hypertension, tachycardia, palpitations, sweating, headaches, nausea, and anxiety. (4, 9, 25, 26, 33, 34) Some patients may also exhibit symptoms related to tumour mass effect, particularly in cases of extra-adrenal paragangliomas. Although most cases are symptomatic, incidental diagnoses occur, especially in patients with a known genetic predisposition undergoing routine surveillance. (10, 20, 35)

In children and adolescents, the anatomical distribution of PGLs differs from that in adults. (6) Approximately 70–80% of tumours are located in the abdomen, with the majority of these arising from the adrenal medulla. Extra-adrenal abdominal paragangliomas account for around 15–20%, often located near the aorta or organ of Zuckerkandl. Pelvic paragangliomas are less common, representing about 5–8%, while head and neck paragangliomas, typically non-functional, occur in approximately 5–10% of paediatric cases. Multifocal and bilateral disease is more frequent in children, particularly in those with underlying genetic pathogenic variants. (6, 8, 9, 25)

The diagnosis of paediatric PGL involves multiple complementary modalities. Clinical evaluation, including detailed family and personal history with physical examination, is essential to assess symptoms, blood pressure variability, and potential syndromic features.

Biochemical testing, primarily measuring plasma-free or urinary metanephrines and normetanephrines, is the gold standard for biochemical confirmation. (36, 37)

Imaging studies, including abdominal MRI and functional imaging such as somatostatin receptor (SSTR)-directed PET/CT (such as [68Ga]Ga-DOTA-TOC/-TATE PET/CT) or [18F]F-DOPA PET/CT, aid in tumour location and staging. (11, 38-40)

Genetic testing is a critical component of the diagnostic workup, as most paediatric PGLs are associated with germline pathogenic variants. (11) Given the high prevalence of hereditary cases, genetic counselling and comprehensive molecular profiling are strongly recommended to guide management and surveillance strategies. (11, 41)

Management by a multidisciplinary team (MDT) following a MDT discussion including medical oncologists, is highly recommended in paediatric patients with suspected PGL. (42-44) *[Level V; Grade A]*

3.2 Clinical evaluation and laboratory assessment

A comprehensive clinical evaluation includes a detailed personal and family medical history, with a focus on symptoms of catecholamine excess, blood pressure variability, and features suggestive of hereditary syndromes. Physical examination should include evaluation of growth parameters (weight, height, body mass index), cardiovascular status, neurological findings, and cutaneous or phenotypic features suggestive of syndromic disease (e.g. café-au-lait macules). Abdominal palpation should be performed to assess for mass lesions. *[Level V; Grade A]*

Laboratory workup should include a complete blood count, renal and liver function tests, serum electrolytes, and coagulation parameters to assess tumour-related metabolic or potential organ dysfunction. *[Level V; Grade A]*

Biochemical confirmation is achieved through measurement of plasma-free metanephrines, normetanephrines, and 3-methoxytyramine, or urinary metanephrines and normetanephrines. (Table 2) Plasma-free metanephrines are generally preferred, particularly in high-risk patients under surveillance programs, as they offer higher sensitivity for detecting early or small

tumours. However, most evidence supporting the superiority of plasma measurements is derived from adult cohorts, and data in children remain limited. (11, 36, 37, 45-50) *[Level IV; Grade A]*

Plasma-free 3-methoxytyramine measurement is recommended for detecting dopamine-producing tumours, which are more commonly associated with somatic *SDHB* mutations or pathogenic *SDHB* germline variants, head and neck paragangliomas (HNPGLs), and tumours with a higher metastatic potential. (51, 52) *[Level IV; Grade B]*

Table 2. Recommended Biochemical Testing in Paediatric PGL

Test	Indication	Notes
Plasma-free metanephrine and normetanephrine	First-line test for suspected PGL, especially in high-risk/genetic cases	Highest sensitivity; preferred in surveillance and early detection; most evidence from adult cohorts
Urinary free metanephrine and normetanephrine	Alternative in younger children or when blood sampling is difficult	Requires age-adjusted reference ranges; lower sensitivity vs plasma
Plasma 3-methoxytyramine	Noradrenergic tumours, known *SDHx* pathogenic variants, metastatic disease surveillance	Marker of dopaminergic activity; associated with higher metastatic potential

Overnight, first morning, or spot urinary free or fractionated normetanephrines and metanephrines can be used as an alternative - using age-appropriate reference intervals (Appendix 2) - particularly in younger children where blood draws may be challenging or distressing. (11, 50, 53) *[Level IV; Grade B]*

Mass spectrometry, particularly liquid chromatography–tandem mass spectrometry (LC-MS/MS), is the preferred method for analysing plasma-free metanephrines and normetanephrines due to its superior specificity and accuracy compared to immunoassays. (11, 54-57) This technique allows for the detection of low-concentration metabolites and provides a more precise assessment of catecholamine secretion patterns in PGLs. Age- and sex-specific reference intervals for plasma concentrations of (nor)metanephrines are important for the correct interpretation. (46, 49, 58, 59) *[Level IV; Grade B]*

Blood sampling should be performed in a stress-free environment, preferably through an indwelling intravenous catheter after 20–30 minutes of supine rest, as sympathetic activation can lead to false-positive results. (11, 36, 60-63) *[Level IV; Grade A]*

Dietary restrictions, particularly for catecholamine precursors such as caffeine, bananas, and chocolate, should be observed for at least 12 hours or overnight prior to plasma 3-methoxytyramine testing. (11, 57, 64) *[Level V; Grade B]*

Given the variability in catecholamine secretion, repeat testing may be necessary in cases with borderline biochemical results, typically defined as levels less than twofold above the upper reference limit in a single metabolite, and in patients with low pre-test probability of PGL. (11, 57, 65) *[Level V; Grade A]*

Serum Chromogranin A may serve as an additional biomarker (for tumour activity), particularly in cases with non-functional or minimally functional tumours; however, its diagnostic performance is limited by low sensitivity and specificity, and it has not been validated in paediatric PGL. *[Level V; Grade C]*

3.3 Imaging

3.3.1 Primary tumour and its loco-regional tumour extension

The initial imaging approach for paediatric PGL focuses on the precise localization of the primary tumour and assessment of local invasion. Ultrasound of the abdomen and neck is a valuable first-line, non-invasive screening tool to evaluate adrenal glands, abdominal masses, and cervical paragangliomas. *[Level V; Grade A]*

Additionally, a chest X-ray may be performed early in the diagnostic process to evaluate for pulmonary lesions, although it has limited sensitivity for small lesions. *[Level V; Grade C]*

For comprehensive assessment, following an abdominal and pelvic US, a magnetic resonance imaging (MRI) is the preferred cross-sectional imaging modality due to its high soft-tissue contrast and avoidance of ionizing radiation. (32, 39, 40) The standard imaging sequence should begin with an abdominal and pelvic MRI, given that the majority of PGLs in children are intra-abdominal. (11) If no lesion is detected, skull base and neck MRI should follow to evaluate for extra-adrenal head and neck paragangliomas. (11, 66) *[Level IV; Grade A]* Contrast-enhanced MRI provides superior anatomical resolution and is recommended for assessing tumour

characteristics, including size, vascular involvement, and potential infiltration of surrounding structures.

When MRI is contraindicated or unavailable, computed tomography (CT) with contrast serves as an alternative imaging tool, offering high-resolution detail of both adrenal and extra-adrenal tumours. (11, 32, 39, 40, 67) *[Level IV; Grade B]*

For loco-regional staging, imaging should assess potential tumour invasion into adjacent structures, regional lymph node involvement, and vascular encasement. *[Level V; Grade A]*

Functional imaging complements MRI/CT and identifies biologically active tumour tissue, supports whole-body staging, and informs theranostic eligibility. (11) It should be considered particularly in suspected multifocal/metastatic disease, extra-adrenal tumours, high-risk genotypes (*SDHx*), or when results of biochemistry/anatomical studies are inconclusive. Selection should be guided primarily by genetic background, tumour site, and local availability. (Table 3) (11, 45) *[Level IV; Grade B]*

The following functional imaging strategies are recommended based on genotype and clinical context:

- SSTR-directed PET/CT (such as [68Ga]Ga-DOTATATE) is the preferred modality for whole-body staging especially in *SDHx*-associated tumours, head and neck paragangliomas, and metastatic disease, given its high somatostatin receptor affinity and excellent sensitivity. (38, 68-70) *[Level IV; Grade B]*
- For patients with *VHL*-associated PGL or cluster 2 kinase signalling mutations or germline pathogenic variants (e.g., *RET*, *NF1*) [18F]F-DOPA PET/CT is typically favoured, particularly for adrenal PGL and confirmation of sporadic PGL. (11, 71) *[Level IV; Grade B]*
- [18F]F-FDG PET/CT should be considered in rapidly progressive, poorly differentiated, or biochemically active tumours, and is particularly useful in *SDHB*-associated PGL due to the accelerated glucose phosphorylation seen in these tumours. It is also a valuable alternative when SSTR-directed or [18F]F-DOPA PET/CT is unavailable. (38, 68-70, 72) *[Level IV; Grade B]* Noteworthy, brown fat activation in patients with high catecholamine burden as well as thyme or endplate uptake in children may generate false positive findings.
- In sporadic cases or when genetic status is unknown, SSTR-directed PET/CT remains the first-line modality, with [18F]F-DOPA PET/CT or [123I]I-

Metaiodobenzylguanidine (MIBG) scintigraphy as alternatives depending on availability and clinical indication. (71, 73) *[Level IV; Grade B]*

- [123I]I- or [131I]I- MIBG scintigraphy may be useful in selected cases, particularly when radionuclide therapy with [131I]I-MIBG is under consideration. However, due to its lower sensitivity, especially in small, extra-adrenal, or *SDHx*-related tumours, MIBG should only be used when PET-based modalities are unavailable or for specific therapy planning. (38, 73) *[Level V; Grade B]*

Whenever feasible, functional imaging should be performed prior to surgery to ensure comprehensive disease staging and guide operative planning, particularly in children at risk of multifocal or metastatic disease. (11) *[Level V; Grade A]*

Table 3. Functional Imaging in Paediatric PGL – genotype-/site-first selection

Genetic background/clinical context	**Preferred functional imaging**	**Acceptable alternatives / when to use**	**Primary purpose(s)/notes**
SDHx-related PGL	[68Ga]Ga-DOTA-SSA PET/CT	[^{18}F]F-FDG PET/CT (aggressive/rapidly progressive disease); [^{18}F]F-DOPA PET/CT (if DOTA-SSA unavailable	Highest sensitivity for *SDHx*, incl. metastatic & head/neck sites; FDG not first-line but helpful for aggressive biology
Head & neck PGL (parasympathetic, often non-secretory; many *SDHx*)	[68Ga]Ga-DOTA-SSA PET/CT	-	DOTA-SSA outperforms other tracers for HNPGL localization and staging
Non-*SDHx* adrenal PGL (incl. *VHL*, *RET*/MEN2, *MAX*, *TMEM127*; sporadic)	[18F]F-DOPA PET/CT	[^{68}Ga]Ga-DOTA-SSA PET/CT (similar sensitivity in metastatic non-*SDHx* adrenal PGL); [^{123}I]I-MIBG scintigraphy (if considering MIBG therapy)	FDOPA generally most sensitive for adrenal PGL and small-volume disease; choose DOTA-SSA or FDOPA pragmatically where similar

Metastatic non-*SDHx* adrenal PGL	[18F]F-FDG PET/CT or [68Ga]Ga-DOTA-SSA PET/CT	Selection based on availability and clinical question (staging vs theranostics)	Adult evidence suggests similar sensitivity; tailor to downstream therapy (e.g., PRRT eligibility).
Unknown/negative germline PV, noradrenergic phenotype, extra-adrenal location suspected	[68Ga]Ga-DOTA-SSA PET/CT	[^{18}F]F-DOPA PET/CT (if adrenal primary more likely)	While genetics pending, use genotype-/site–based likelihood; escalate to whole-body staging when risk higher
Aggressive, poorly differentiated, rapidly progressive disease (any genotype)	[18F]F-FDG PET/CT	Add DOTA-SSA or FDOPA as per genotype/site to complete staging	FDG reflects glycolytic activity; not first-line for localization but useful in high-grade/aggressive behaviour
Theranostic selection for MIBG therapy	[123I]I-MIBG scintigraphy	-	Diagnostic role mainly to confirm avidity for [^{131}I]I-MIBG therapy; lower sensitivity than PET for localization.

The differential diagnosis of paediatric PGL depends on the anatomical location of the tumour and clinical context. In children with an adrenal mass, key differential diagnoses include neuroblastoma (particularly in younger children and especially when MIBG scintigraphy is positive), ganglioneuroma, adrenocortical tumours, and rare lesions such as desmoid tumours, mature teratomas, and adrenal cysts. While biochemical testing, tumour markers, and radiologic features—such as calcifications, vascularity, and functional imaging characteristics—can provide diagnostic clues, they may not reliably distinguish PGL from neuroblastoma in all cases. (11) Functional imaging and catecholamine profiles may overlap, and definitive diagnosis often relies on a combination of clinical presentation, patient age, and a comprehensive evaluation involving imaging, biochemical, and pathological assessments. (74) At extra-adrenal sites, the differential diagnosis may include soft tissue sarcomas, vascular malformations, and rare neurogenic tumours.

3.3.2 Distant metastasis

In paediatric patients with high-risk features – including recurrent disease, large tumour burden, aggressive clinical behaviour, or known genetic germline pathogenic variants (e.g. *SDHB*) – a

comprehensive evaluation for distant metastases is strongly recommended. (11) *[Level V; Grade A]* The most common metastatic sites include the lungs, liver, bones, and lymph nodes.

Whole-body MRI is particularly useful for detecting skeletal metastases in non-secreting tumours, offering high sensitivity without exposure to ionizing radiation. (11, 36, 39) *[Level V; Grade B]*

For functional imaging, modality selection should follow a risk-adapted and genotype-informed approach:

- SSTR-directed PET/CT is generally preferred for whole-body staging, especially in *SDHx*-associated tumours and metastatic disease, due to its high sensitivity for somatostatin receptor-positive lesions. (11, 69, 72) *[Level IV; Grade B]*
- [18F]F-FDG PET/CT may provide additional or superior information in tumours with high proliferative activity, poor SSTR expression, or high 3-methoxytyramine, and is particularly useful in aggressive or rapidly progressing disease, including those suspected to be *SDHB*-related. (11, 71, 73) *[Level IV; Grade B]*
- [18F]F-DOPA PET/CT and [123I]I-MIBG scintigraphy can be considered in selected cases, particularly in tumours with kinase signalling alterations (e.g., *RET*, *NF1*) or sporadic PGLs, where these tracers may provide enhanced localization based on tumour biology. (11, 69, 71, 73) *[Level IV; Grade C]*

In the absence of genetic testing results, imaging strategies should be guided by the biochemical phenotype, tumour location, and clinical presentation. For noradrenergic tumours (elevated normetanephrines without elevated metanephrine), [68Ga]Ga-DOTATATE PET/CT is generally the preferred functional imaging modality. In contrast, for tumours with and adrenergic phenotype (characterized by significant elevation of plasma metanephrine, with or without coexisting normetanephrine elevation, [18F]F-DOPA PET/CT or [123I]I-MIBG imaging may be more appropriate. This biochemical classification helps inform both imaging selection and perioperative planning. (11, 38, 68) *[Level IV; Grade A]*

When feasible, comparing multiple imaging modalities within the same patient may support both initial staging and long-term follow-up strategies; however, in paediatric patients, this approach must be carefully balanced against cumulative radiation exposure, favouring modalities such as MRI and PET-based techniques with lower radiation doses whenever possible. *[Level V; Grade C]*

In patients with persistent elevation of catecholamine metabolites (e.g. plasma or urinary metanephrines) after surgery, early post-operative imaging to assess for residual or metastatic disease is strongly recommended. *[Level V; Grade A]*

3.4 Genetic testing

Approximately 80% of paediatric PGLs are associated with germline pathogenic variants in susceptibility genes, most commonly affecting the pseudohypoxic pathway genes (e.g., *VHL*, *SDHx*, *EPAS1*). Other implicated genes include those involved in kinase signalling (e.g., *RET*, *NF1*, *MAX*, *TMEM127*). (6, 9, 19) Given this high prevalence of hereditary PGL in children and adolescents, genetic testing should be done in all children diagnosed with PGL, given the potential implications for diagnosis, risk stratification, long-term management, and familial screening. (75) In clinical practice, genetic testing should be integrated into the diagnostic workup for paediatric PGL. (11) However, in accordance with genetic diagnostic regulations, genetic counselling is recommended before testing, with the final decision resting with the patient or their legal representatives. In cases where a pathogenic variant is identified, cascade testing should be offered to at-risk family members to enable early diagnosis and appropriate surveillance for asymptomatic carriers. *[Level IV; Grade A]*

Additionally, in cases where no pathogenic variant is detected, methylation analysis or whole-exome/genome sequencing may be considered to identify novel or rare genetic drivers. (11, 76) *[Level V; Grade B]*

As genetic findings have therapeutic and prognostic relevance, an interdisciplinary approach involving paediatric oncologists, endocrinologists, pathologists, geneticists, and genetic counsellors (subject to availability) is recommended to optimize patient care and ensure informed decision-making regarding genetic testing and subsequent management. *[Level IV; Grade A]*

3.5 Biopsy

Biopsy in paediatric PGL is strongly discouraged and should be limited to exceptional cases, such as unresectable tumours where the diagnosis remains uncertain and could significantly impact treatment strategy. *[Level V; Grade E]*

The indication for biopsy must be determined by a MDT. The gold standard remains primary microscopic complete tumour resection without prior biopsy, based on clinical, biochemical, and imaging findings. Biopsy carries significant risks, including catecholamine crisis and tumour seeding, and should only be performed after appropriate pre-procedural blockade and in specialized centres. *[Level V; Grade A]*

The rare indications for tumour biopsy include:

- Unresectable or metastatic disease, when histological confirmation is necessary for treatment planning.
- Atypical imaging findings, where differential diagnoses such as neuroblastoma, other neuroendocrine tumours, or adrenocortical tumours are under consideration. However, in such cases, primary surgical resection should be prioritized over biopsy if the tumour is amenable to wide en-bloc complete tumour resection.
- Non-functioning tumours with negative biochemical work-up, where imaging suggests a possible PGL but direct complete tumour removal is not feasible.

[Level V; Grade A]

Biopsy approach and precautions:

If biopsy is deemed necessary, after MDT discussion, the procedure must be performed with strict hemodynamic preparation and peri-procedural safety measures, ideally with an anaesthesiology team, with expertise in this disease, including:

- Execution by an experienced MDT including a radiologist, paediatric surgeon, anaesthesiologist, and endocrinologist, within a specialized paediatric centre equipped to manage PPGL-specific risks.
- Pre-procedural alpha-adrenergic blockade for a minimum of 7–14 days, in line with preoperative preparation protocols (cf. preoperative preparation).
- Use of minimalist image-guided core-needle biopsy (18G) under careful anaesthetic and cardiovascular monitoring.

[Level V; Grade A]

Contraindications:

- Biopsy is not indicated when the tumour is resectable, or when PPGL is biochemically and radiologically likely and surgical excision can be safely achieved. *[Level IV; Grade E]*

Given the risks associated with biopsy, histopathological confirmation should be sought only in select cases where surgical resection is not feasible, and alternative diagnoses must be ruled out before initiating systemic treatment. *[Level IV; Grade A]*

3.6 Histopathology

Careful histopathological evaluation should be undertaken, and a(n) (inter)national reference pathology review in addition to the local pathological analysis is strongly recommended. *[Level V; Grade B]*

Histopathological evaluation of paediatric PGLs follows the criteria established by the WHO classification, which categorize PGLs based on their anatomical location and underlying molecular alterations, and includes assessment of tumour architecture, cellular morphology, mitotic index, vascular and capsular invasion, and necrosis. (3) In addition, recently the International Collaboration on Cancer Reporting (ICCR) has published a dataset for the reporting of these tumours. (77) Resected tumours should be classified using the TNM (Tumour-Node-Metastasis) staging system (Appendix 1), which provides prognostic information based on tumour size, nodal involvement, and presence of distant metastases. (78) *[Level IV; Grade A]*

Parameters for histopathological assessment include:

- Tumour size and location (adrenal vs. extra-adrenal involvement)
- Resection margin status (R0, R1, R2) to determine completeness of excision
- Presence of a lymphovascular and perineural invasion, which may indicate more aggressive tumour behaviour
- Mitotic activity and Ki-67 proliferation index, which can provide insights into tumour growth rate and potential for recurrence.
- Presence of necrosis or haemorrhage, which can be seen in more aggressive lesions

[Level IV; Grade A]

Immunohistochemistry (IHC) plays a critical role in confirming the diagnosis of PGL and identifying underlying genetic disorders.

IHC markers include:

- Chromogranin A and Synaptophysin – Neuroendocrine markers confirming chromaffin cell origin
- GATA3 – A transcription factor that can be used as marker for PGL, although not specific
- Tyrosine hydroxylase (TH) – A key enzyme in catecholamine synthesis, useful for confirming catecholamine-producing tumours including both PGL and neuroblastoma
- S100 and/or SOX10 – Highlights sustentacular cells, which are often preserved in benign PGLs but may be reduced in more aggressive tumours
- SDHB and SDHA IHC – Loss of SDHB expression suggests an underlying *SDHx* pathogenic variant, particularly in *SDHB*- or *SDHC*-mutated tumours; loss of SDHA expression suggests an underlying *SDHA* pathogenic variant
- FH- and 2SC IHC for the detection of fumarate hydratase-associated PGL, in the context of hereditary leiomyomatosis and renal cell carcinoma (HLRCC) syndrome
- Carbonic anhydrase IX (CAIX) can be regarded as a surrogate biomarker for PGL in VHL disease

[Level V; Grade A]

All PGLs are now considered to have malignant potential, and histopathological markers are used to stratify risk.

Pathological features suggestive of aggressive or metastatic potential include:

- High Ki-67 index (>5%)
- Increased mitotic count (>3 per 10 HPF [high-power fields])
- Presence of necrosis and capsular invasion
- Loss of sustentacular cells on S100 staining
- SDHB-negative staining.

Several histopathological grading systems have been proposed to predict the metastatic potential of PGLs:

- PASS (Pheochromocytoma of the Adrenal Gland Scaled Score) (79)– Primarily used in adult PGLs, evaluating factors such as invasion, necrosis, and mitotic rate. If score >4, in favour of a malignant disease.
- GAPP (Grading of Adrenal Pheochromocytoma and Paraganglioma) (80)– Considers histologic and immunohistochemical markers to stratify malignancy risk
- COPPS (Composite Pheochromocytoma/Paraganglioma Prognostic Score) (81)– Incorporates genetic, biochemical, and histopathologic factors to refine prognosis

While these scoring systems may provide useful information, they have not yet been fully validated in paediatric populations, and their predictive value in children remains an area of ongoing research. In addition, they are currently not endorsed by the WHO. (82) *[Level IV; Grade C]*

There are many clues to genetic subtypes of PGL, including extra-adrenal tumour location and loss of SDHB staining in tumours with *SDHx*, especially *SDHB* variants; bilateral occurrence with highly vascular tumours with clear cell morphology in VHL-associated PGL; and bilateral multifocal with high catecholamine production in PGL with *RET* variants in MEN2 syndrome.

In addition, IHC may not only serve diagnostic purposes, but also contribute to prognosis and prediction:

- Ki-67 proliferation index – Low in most PGLs but may be elevated in tumours with higher metastatic potential
- SSTR2 labelling may predict the use of somatostatin inhibitors in tumours that are not amenable to surgery (83)
- Loss of ATRX staining at IHC may indicate the presence of *ATRX* mutations, associated with worse prognosis

Comprehensive histopathological evaluation, combined with IHC and genetic analysis, is essential for determining tumour behaviour, guiding follow-up strategies, and tailoring patient management.

3.7 Molecular pathology / Analysis of potential therapeutic targets

Molecular profiling has significantly advanced the understanding of paediatric PGL, enabling refined risk stratification and identifying potential therapeutic targets. Paediatric PGLs frequently harbour germline pathogenic variants or somatic mutations in susceptibility genes,

with up to 80% of cases linked to well-characterized molecular pathways. These include pseudohypoxic signalling (*VHL*, *SDHx*, *EPAS1*, *FH*), kinase-driven signalling (*RET*, *NF1*, *TMEM127*, *MAX*, *HRAS*), and Wnt pathway dysregulation (*CSDE1*, *MAML3*).

Somatic next-generation sequencing (NGS) is increasingly proposed for comprehensive genomic profiling, particularly in patients with aggressive or metastatic disease. Methylation analysis may further aid in classifying tumours with SDH deficiency, which are characterized by distinct epigenetic signatures. IHC serves as a practical adjunct, with SDHB staining loss indicating *SDHx*-related disease and ATRX loss suggesting a more aggressive phenotype. These molecular insights help guide both surveillance strategies and therapeutic decision-making. *[Level V; Grade B]*

Targeted treatment approaches are being explored based on molecular subtyping. HIF2α inhibitors, such as belzutifan, are under investigation for *VHL*- and *EPAS1*-mutated tumours. Tyrosine kinase inhibitors (TKIs) may benefit patients with *RET* or *NF1* pathogenic variants, while peptide receptor radionuclide therapy (PRRT) is considered for tumours demonstrating strong somatostatin receptor (SSTR) expression. These emerging treatment options highlight the evolving landscape of precision medicine in PGL.

3.8 Additional assessments

3.8.1 Cardiovascular Evaluation

Given the excessive catecholamine secretion characteristic of PGL, cardiovascular assessment is a critical component of the diagnostic and preoperative workup. Persistent or paroxysmal hypertension, tachyarrhythmias, and catecholamine-induced cardiomyopathy are major concerns in paediatric PGL patients.

All patients should undergo blood pressure monitoring to assess the extent of hypertension, which can be sustained or episodic. Echocardiography is recommended to evaluate cardiac function, particularly for signs of left ventricular hypertrophy or catecholamine-induced cardiomyopathy. Electrocardiography (ECG) should be included in the baseline cardiovascular workup. Holter monitoring is indicated in patients with dual-secreting tumours (elevated normetanephrine and metanephrine), very high catecholamine levels, or clinical suspicion of arrhythmia, to assess for paroxysmal arrhythmia or myocardial strain. *[Level IV; Grade B]*

3.8.2 Metabolic and Endocrine Assessment

Hyperglycaemia is a potential complication due to catecholamine-induced insulin resistance. Fasting blood glucose and HbA1c should be measured, particularly in patients with persistent symptoms of hyperglycaemia. Additionally, adrenal function should be evaluated including morning serum cortisol and ACTH levels, to assess adrenal insufficiency risk, even in unilateral tumours. In cases where bilateral adrenalectomy is required, adrenal function needs to be supplemented. *[Level IV; Grade A]*

3.8.3 Neurocognitive and Psychological Impact

Children with hereditary PGL syndromes may experience neurocognitive and psychological challenges, particularly in cases with recurrent or metastatic disease. Anxiety disorders, panic attacks, and emotional lability may result from prolonged catecholamine excess. A referral to clinical psychology or neurocognitive evaluation should be considered for patients experiencing significant emotional distress or cognitive difficulties. *[Level V; Grade B]*

4. Treatment details

4.1 General considerations

- MDT discussion is mandatory with surgeons, nuclear medicine specialists, paediatrician, medical oncologists, and endocrinologists before, at diagnosis, and during therapy. (11) *[Level IV; Grade A]*
- Psychosocial support must be offered at diagnosis and during therapy and follow-up. *[Level IV; Grade B]*
- Patients/families should be invited to participate in a prospective clinical trial (or in a registry) when available, with data collection in national or international databases to improve the knowledge of this disease. (11) *[Level V; Grade A]*
- Patients/families should be invited to participate in molecular analyses/biobanking projects when available, with collection of biological samples to improve the knowledge of this disease. (11) *[Level V; Grade B]*
- Surgery, medical management, focal therapies, and watch-and-see strategies should be considered as part of individualized treatment planning.

4.2 Watchful Waiting

Watchful waiting, or a "wait and see" strategy, is generally not standard practice in the management of paediatric PGL due to the high prevalence of hereditary disease, greater risk of multifocality and recurrence, and limited paediatric-specific data supporting this approach. However, in adult patients with HNPGLs, active surveillance is an established first-line option, particularly for small, asymptomatic tumours with indolent growth patterns. This strategy aims to minimize the morbidity associated with intervention in anatomically sensitive areas and is supported by long-term outcome data. While not routinely recommended in children, awareness of this adult practice may provide additional context for MDT discussions in highly selected paediatric cases. The decision to pursue a watchful waiting approach should be individualized, made within the framework of an experienced MDT, and accompanied by careful clinical and biochemical monitoring. (44, 84-87) *[Level V; Grade B]*

4.3 Preoperative Management

Preoperative management is essential to minimize perioperative complications in paediatric patients with PGL, given the risk of catecholamine-induced cardiovascular instability. The main goals are to achieve adequate alpha-adrenergic blockade, optimize intravascular volume, and mitigate hypertensive crises during surgery.

4.3.1 Alpha-Adrenergic Blockade

The cornerstone of preoperative management is alpha-adrenergic blockade, which should be initiated at least 7–14 days before surgery to allow adequate hemodynamic stabilization. (11, 36, 88)

- Phenoxybenzamine: Initial dose of 0.2 mg/kg/day, divided into two doses, and titrated every 2–3 days to achieve adequate blood pressure control and tolerability
- Doxazosin: Starting dose of 0.5–1 mg/day, increasing every 3–5 days to a target dose of 2–4 mg/day

Clinical targets include maintenance of blood pressure below the 90th percentile for age and height and the presence of mild orthostatic hypotension without significant symptoms. (15, 89, 90)

[Level IV; Grade A]

4.3.2 Beta-Adrenergic Blockade

Beta-blockers should never be initiated before adequate alpha blockade, as this can lead to unopposed alpha-mediated vasoconstriction and hypertensive crisis. Beta-blockers (e.g., propranolol, atenolol, metoprolol) should be introduced only in patients with persistent tachycardia after alpha blockade is well established. (11, 36, 91-93)

- Propranolol: 0.5–1 mg/kg/day, divided into 2–3 doses
- or Atenolol: 0.5–1 mg/kg once daily, titrated as needed

[Level V; Grade B]

4.3.3 Calcium Channel Blockers

In patients who cannot tolerate alpha-blockade, or in those with refractory hypertension, calcium channel blockers such as amlodipine or nicardipine can be considered as alternative or adjunct therapy. These agents may also be beneficial for blood pressure stabilization in patients with significant cardiovascular comorbidities. (36, 88) *[Level V; Grade B]*

4.3.4 Volume Expansion and Dietary Considerations

Due to chronic catecholamine-induced vasoconstriction, paediatric PGL patients frequently present at diagnosis with intravascular volume depletion, increasing the risk of hypotension following tumour resection. Appropriate preoperative volume expansion is therefore essential to ensure hemodynamic stability during and after surgery (11) *[Level IV; Grade B]:*

- Adequate oral fluid intake should be encouraged and intravenous fluid supplementation considered in cases of poor intake gastrointestinal symptoms, or more advanced volume depletion.
- A high-sodium diet (typically 5–10 g/day, equivalent to 4-6 mmol/kg/day) should be recommended for at least 3–5 days preoperatively to promote volume expansion.
- Preventive measures against constipation – such as dietary fibre, stool softeners, or osmotic laxative – should be implemented proactively, particularly in patients receiving alpha-adrenergic blockade, which can contribute to reduced gut motility and constipation.

4.3.5 Preoperative Cardiovascular Monitoring

Patients should undergo a comprehensive cardiovascular assessment before surgery, including:

- Echocardiography to evaluate cardiac function and detect catecholamine-induced cardiomyopathy
- Electrocardiography (ECG) for baseline rhythm assessment
- Holter monitoring selectively in patients with very high catecholamine levels, dual secretion, or symptoms suggestive of arrhythmia
- Blood pressure monitoring to ensure optimal preoperative control

[Level V; Grade B]

4.3.6 Anaesthetic Considerations and Intraoperative Monitoring

Before surgery, close collaboration between the paediatric oncology, endocrinology, surgical, and anaesthetic teams is critical. Anaesthetic induction and maintenance require careful hemodynamic control, with agents that minimize catecholamine release and prevent excessive hypotension post-tumour removal.

- Intraoperative hemodynamic monitoring and control: Patients are at risk of hypertensive crises during tumour manipulation and hypotension following tumour removal due to catecholamine withdrawal. *[Level V; Grade A]*
- Close coordination between the surgical and anaesthetic teams: Intraoperative agents such as sodium nitroprusside, esmolol, or magnesium sulfate may be required to manage blood pressure, particularly during the vascular section and tumour mobilization, when catecholamine surges and hemodynamic instability are most likely to occur.
- Adequate fluid management: Given that many patients are chronically volume depleted due to prolonged catecholamine excess, careful volume replacement is necessary.

4.3.7 Preoperative Management of Bilateral Adrenal Tumours

In cases of bilateral pheochromocytomas requiring total adrenalectomy, perioperative glucocorticoid and mineralocorticoid replacement should be initiated to prevent post-surgical adrenal insufficiency. Cortical-sparing adrenalectomy may be considered in select cases to preserve endogenous adrenal function. *[Level IV-V; Grade B]*

4.4 Surgery

Surgical resection remains the definitive treatment for paediatric PGL, providing the highest potential for cure while minimizing recurrence and metastatic progression. (8, 9) The primary

surgical goal is complete tumour excision with negative (R0) margins, which may be achieved via minimally-invasive or open approaches, depending on tumour location, size (< 5cm), and radiologic features. (94-96) However, standardized radiological criteria to predict resectability are currently lacking, and no specific recommendations exist to guide the choice of surgical approach based solely on imaging.

Surgical Considerations

- Adrenal pheochromocytomas: Laparoscopic or robotic adrenalectomy is the preferred technique for tumours without imaging evidence of local invasion or surgical complexity, provided it is performed in centres with expertise in paediatric endocrine and oncologic surgery. (11) *[Level IV; Grade A]*
- Extra-adrenal paragangliomas: These tumours often require open resection, particularly when they are large, invasive, or adjacent to critical vascular structures. *[Level IV; Grade B]*
- Bilateral disease: Cortical-sparing adrenalectomy, at least on one side, should be considered in hereditary cases to preserve adrenal function and reduce the risk of lifelong adrenal insufficiency. This approach is particularly appropriate in patients with *VHL* or *RET* pathogenic variants, who have a high likelihood of bilateral disease. However, cortical-sparing surgery is contraindicated in patients with *SDHB* pathogenic variants, due to the significantly increased risk of recurrence and malignancy. (11, 97, 98) *[Level IV-V; Grade B]*
- Regional lymph node dissection: Should be performed when nodal involvement is suspected or confirmed on imaging, particularly in *SDHB*-mutated tumours, which carry a higher risk of metastatic spread. Surgical management could follow recommendations established for paediatric sarcoma. *[Level V; Grade B]*

In selected patients with metastatic disease, surgical resection or local therapies on focal distant sites (surgery, stereotaxic radiotherapy, thermal ablation, chemoembolization) may still play a role in reducing tumour burden and catecholamine secretion, thereby alleviating symptoms and improving biochemical control. (99-101) Particularly when all known lesions appear surgically accessible, complete resection of primary and metastatic sites may be considered within a multidisciplinary treatment strategy, though this should be carefully weighed against expected morbidity and overall disease course. Surgery in this context is not curative but can provide clinical benefit in appropriately selected cases. *[Level V; Grade B]*

Flowcharts of the recommended diagnostic and therapeutic approaches in paediatric PGL are presented in Appendix 3.

4.4.1 Immediate Postoperative Monitoring and Considerations

- Close monitoring for hypotension, which can occur due to the sudden loss of catecholamine-mediated vasoconstriction following tumour removal. *[Level V; Grade A]*
- Risk of hypoglycaemia, particularly in younger children, due to abrupt cessation of catecholamine-driven gluconeogenesis. *[Level V; Grade B]*
- Electrolyte imbalances, especially in cases of bilateral adrenalectomy, requiring careful glucocorticoid and mineralocorticoid replacement therapy and close monitoring. *[Level IV; Grade A]*
- Transient adrenal insufficiency has been reported in rare cases following unilateral adrenalectomy, particularly in patients with preoperatively high catecholamine levels, potentially due to suppression of the contralateral adrenal gland. Although not routinely expected, short-term glucocorticoid replacement may be considered in symptomatic patients or when there is biochemical evidence of adrenal insufficiency during the postoperative period. *[Level V; Grade C]*

4.5 Observation and Adjuvant Therapies

In paediatric PGL, the role of adjuvant therapy following resection of localized disease is limited and primarily guided by extent of surgical resection and clinical behaviour of the tumour. In patients with complete resection (R0), no adjuvant therapy is indicated, regardless of genetic status or biochemical profile. *[Level IV; Grade B]*

Similarly, for patients with microscopically positive margins (R1), routine adjuvant treatment is not recommended, as there is currently no evidence supporting improved outcomes in this setting. *[Level V; Grade D]*

In cases where macroscopically incomplete resection (R2) has occurred, the first step should be to evaluate the feasibility of repeat surgery with curative intent. If re-resection is not possible, a period of close observation is advised, as some residual lesions may remain biochemically

stable and clinically indolent for extended periods. Treatment should not be initiated solely on the basis of residual disease, but only if clear tumour progression or new symptoms occur. *[Level V; Grade B]*

If local progression is documented during follow-up, local therapies such as re-surgery, thermal ablation, stereotactic radiotherapy, or external beam radiotherapy may be considered, depending on the anatomical site and multidisciplinary evaluation. In situations where local control cannot be achieved with surgery or focal therapies, systemic medical treatment may be discussed as a last resort, based on the patient's clinical symptoms and tumour behaviour. (11) *[Level V; Grade B]*

This principle also applies to metastatic disease: given the often slow-growing nature of PGL, even metastatic tumours may remain asymptomatic and stable for years. (102, 103) Therefore, in patients with low tumour burden and slow growing progression, the initial approach to metastatic disease may be active surveillance, with intervention reserved for cases with high tumour burden, clear progression, and/or significant symptoms. (11) *[Level V; Grade A]*

In *SDHB*-associated PGL, MDTs should more proactively evaluate cytoreductive strategies (e.g., debulking surgery or focal therapies), given the higher malignant potential and young age at onset. Decisions should be guided by MDTs with expertise in nuclear medicine, systemic therapies, surgery, and supportive care. *[Level IV; Grade A]*

4.6 Chemotherapy

The role of conventional chemotherapy in paediatric PGL remains highly limited and is generally reserved for cases with high tumour burden and/or progressive metastatic disease that are not amenable to surgical resection, targeted therapy, or radionuclide therapy. Given the indolent nature of many PGLs and their low mitotic activity, chemotherapy is often associated with only modest response rates and is primarily used for tumour stabilization rather than curative intent. *[Level V; Grade B]*

Chemotherapy is therefore not routinely recommended for paediatric PGL but may be considered in the following situations:

- Progressive metastatic PGL, particularly in patients with *SDHB* pathogenic variants, which are associated with a more aggressive clinical course and higher risk of further progression.

- Extensive symptomatic disease burden, where other systemic treatment options have failed or are unavailable.
- Palliative settings, when surgical, targeted, or radionuclide-based approaches are not feasible.

[Level V; Grade B]

The most widely used chemotherapy regimen is the CVD regimen (Cyclophosphamide, Vincristine, Dacarbazine), originally developed in adults with metastatic PGL and sometimes extrapolated for paediatric use:

- Cyclophosphamide: 750 mg/m² IV on day 1 with hydration
- Vincristine: 1.4 mg/m² IV on day 1 (maximum 2 mg/dose)
- Dacarbazine: 600 mg/m² IV on days 1 and 2

Cycles are repeated every 3–4 weeks, depending on tolerance and clinical response. Despite its historical use, CVD chemotherapy rarely results in significant tumour shrinkage but may provide temporary disease stabilization and symptom control, particularly in cases of catecholamine excess. (101, 104-106) *[Level V; Grade C]*

An alternative agent under consideration is temozolomide, an oral alkylating agent. Although data in children are limited, temozolomide has shown activity in adults with metastatic PGL, particularly in tumours harbouring *SDHB* mutations and exhibiting MGMT promoter hypermethylation, a potential biomarker of response. (107, 108) *[Level V; Grade B]*

Chemotherapy therefore remains a non-first-line option and should be reserved for exceptional, highly selected cases of aggressive or rapidly progressing metastatic disease. Given its limited efficacy and significant toxicity, treatment decisions should always be made within a MDT board, ideally in the context of specialized centres or clinical trials. *[Level V; Grade A]*

With the evolution of targeted therapies and PRRT, which offer lower toxicity and more biologically precise mechanisms of action, chemotherapy is increasingly regarded as a last-line intervention.

4.7 Targeted Therapy, Peptide Receptor Radionuclide Therapy, and other Systemic Therapies

The emergence of targeted therapies and nuclear medicine theranostic approaches has provided new avenues for the treatment of progressive or metastatic PGL, particularly in patients with

specific molecular alterations. While conventional chemotherapy has shown limited efficacy, precision medicine strategies offer the potential for improved tumour control with a more favourable toxicity profile. These approaches leverage the distinct molecular and metabolic characteristics of PGLs, guiding treatment based on genetic and imaging findings.

Although clinical experience in the paediatric population remains limited and many therapies are still under investigation or not yet widely available for children, the expanding therapeutic landscape holds significant promise for high-risk and treatment-refractory disease.

4.7.1 Tyrosine Kinase Inhibitors (TKIs)

TKIs target dysregulated kinase pathways in PGL, particularly in tumours with *RET*, *NF1*, or other kinase-activated mutations. While data in paediatric patients are limited, experience from adult PGL and neuroendocrine tumours supports the potential use of TKIs in progressive metastatic disease.

- Sunitinib: A multi-kinase inhibitor that targets VEGFR, PDGFR, and RET. Used for progressive metastatic PGL, particularly in *SDHB*-mutated tumours.
- Cabozantinib: VEGFR and RET inhibitor, with early data suggesting activity in aggressive PGL.
- Selpercatinib and Pralsetinib: Highly selective RET inhibitors, mainly indicated for MEN2-associated PGL or PGL with somatic *RET* mutations.

Use of TKIs requires careful monitoring for hypertension, fatigue, renal dysfunction, and hepatotoxicity. (109, 110) *[Level V; Grade B]*

4.7.2 Hypoxia-Inducible Factor (HIF2α) Inhibitors

Pseudohypoxic PGLs, particularly *VHL*- and *EPAS1*-mutated tumours, may respond to HIF2α inhibitors.

- Belzutifan (HIF2α inhibitor): As of May 14, 2025, the U.S. Food and Drug Administration has approved belzutifan for adult and paediatric patients aged 12 years and older with locally advanced, unresectable, or metastatic PGL. By blocking HIF2α activity, belzutifan reduces hypoxia-driven tumour growth and catecholamine secretion, offering a rationale for its potential use in pseudohypoxic PGLs.

However, no clinical data currently exist in paediatric patients, and the safety and efficacy of belzutifan in children remain unknown. Therefore, this treatment should ideally be considered

only within the context of an investigator-led clinical trial or specialized protocol. (111, 112) *[Level V; Grade C]*

4.7.3 Peptide Receptor Radionuclide Therapy (PRRT)

PGLs often overexpress somatostatin receptors (SSTRs), making them amenable to radionuclide-labelled somatostatin analogues for targeted radiotherapy. (113, 114)

- [177Lu]Lu-DOTATATE: Used in somatostatin receptor-positive metastatic PGL, particularly in *SDHB*-related disease.

PRRT is generally well tolerated and has demonstrated long-term disease stabilization and symptom relief in adult studies, though data in paediatric patients remain limited. (114-116) The efficacy of PRRT depends on high SSTR expression, typically confirmed using SSTR-directed PET/CT prior to treatment. (83) While PRRT provides a biologically targeted treatment option, it carries potential risks, including renal and hematologic toxicity and the possibility pf therapy-related secondary malignancies. (115, 117, 118) *[Level V; Grade B]*

4.7.4 Metaiodobenzylguanidine (MIBG) Therapy

[131I]I-MIBG therapy is a potential option for patients with metastatic PGL demonstrating sufficient tracer uptake on diagnostic scintigraphy. While data in children are limited, retrospective studies suggest disease control in selected cases, particularly in those with biochemically active, symptomatic tumours. (119-121) High-specific-activity formulations have shown promising response rates; however, their availability is currently restricted due to discontinuation in some regions. (122, 123) As not all paediatric PGLs are MIBG-avid, diagnostic [123I]I-MIBG scintigraphy should confirm uptake prior to therapeutic use. [131I]I-MIBG therapy remains the standard radionuclide treatment in routine care and may be considered for MIBG-avid tumours requiring symptom control or systemic disease management. PRRT should be considered only within clinical protocols or following careful multidisciplinary review, particularly when MIBG therapy is unsuitable or unavailable. *[Level IV–V; Grade B]*

Note: The high-specific-activity [^{131}I]I-MIBG formulation (iobenguane, Azedra®), which showed improved tumour targeting, is no longer commercially available; conventional [^{131}I]I-MIBG remains in clinical use.

4.7.5 Metabolic and Epigenetic Therapies

Novel therapies are being explored for *SDH*-deficient PGL, given their distinct metabolic and epigenetic profile.

- DNA methyltransferase inhibitors (e.g., Decitabine): Target hypermethylation seen in *SDHB*-mutated tumours. (124-126)
- Glutaminase inhibitors (e.g., telaglenastat, sirpiglenastat, IACS-6274): Explored in tumours with Krebs cycle dysfunction, such as *SDH*-mutated PGLs. (127)

These emerging therapies offer an alternative approach for patients with *SDHB*-associated metastatic disease, though clinical data in paediatric PGL remain limited. *[Level V; Grade D]*

4.7.6 Immunotherapy

The role of immunotherapy in paediatric PGL is currently experimental. Available data in adults with PGL are limited, and no clinical evidence supports its routine use in children. Given the low tumour mutational burden and the typical immune-cold microenvironment of PGLs, responsiveness to checkpoint inhibitors or other immunotherapeutic agents is expected to be low. (128)

At present, immunotherapy should not be used outside of a clinical trial, and its application should be limited to highly selected patients within investigator-led or early-phase studies. *[Level V; Grade E]*

The landscape of systemic therapies for PGL is continually evolving, with ongoing research exploring combination approaches and novel biomarkers. Combination strategies, such as TKIs with PRRT or HIF inhibitors with kinase inhibitors, may enhance treatment efficacy by targeting multiple oncogenic pathways simultaneously.

While targeted therapies and theranostic approaches are not yet standard of care for paediatric PGL, they offer promising treatment avenues for patients with progressive, unresectable, or metastatic disease. Given the heterogeneity of PGLs, treatment decisions should be made in MDT boards, especially in such refractory situations, incorporating input from paediatric oncologists, endocrinologists, and nuclear medicine specialists. The availability of these therapies remains largely limited to clinical trials or specialized centres.

4.8 Radiotherapy

The role of radiotherapy (RT) in paediatric PGL is not well established and remains under debate due to PGLs´ slow-growing nature and concerns about radiation-induced late effects, particularly in children. (11, 129, 130) Furthermore, the diverse anatomical locations of PGL represent challenging treatment sites for any local therapy. However, with the use of modern and highly conformal techniques, radiotherapy can be considered as a viable treatment option in second-line therapies or as complementary modality in selected cases, aiming for local tumour control or palliation — including unresectable, advanced, and (oligo)metastatic disease. (11, 93) *[Level V; Grade A]* Notably, in adult patients, radiotherapy is an accepted first-line option for HNPGLs, offering durable local control in anatomically challenging sites; while this approach is not routinely used in children, it may inform MDT decision-making in selected paediatric cases. (85)

The decision to use radiotherapy should be based on a consensus of a MDT board, considering all types of effective treatment strategies and the risk-benefit ratio for each patient.

Possible indications for radiotherapy are:

- Unresectable progressive or symptomatic primary tumours where surgery is contraindicated due to local invasion or critical anatomical constraints. (131-134)
- Symptomatic metastases, particularly threatening or symptomatic bone metastases, where RT can provide palliative pain relief and local disease control. (131-134)
- Progressive residual disease post-surgery, in cases where resection macroscopically incomplete and local recurrence/progression risk is high.
- Rapidly progressive metastatic disease, particularly in cases where systemic options are limited or ineffective. (131-134)

[Level V; Grade B]

Different high conformal radiotherapy techniques and modalities (with limited radiation exposure resulting in potential less severe late effects) are available for treatment of children with PGL.

Regarding external beam radiotherapy, highly conformal photon techniques, such as intensity-modulated radiotherapy or volumetric-modulated arc therapy, are typically used.

Furthermore, proton beam therapy – taking advantage from a particular dosimetric characteristics and improved sparing of adjacent organs at risk – may be an appealing alternative when looking at patients with a curative chance or longer-term prognosis. (135)

Another technique used is stereotactic body radiotherapy, particularly in patients with oligo-metastases. (136)

The radiation dose depends on resectability and target site, particularly if primary disease or metastases need to be treated. In head and neck PGLs, median total doses usually range from 40 Gy to 50.4 Gy using conventional fractionation schemes. (135-137)
In addition, overall intent of treatment – palliative or curative – has to be considered when tailoring radiation strategies.
Apart from external beam radiotherapy, targeted radiotherapy may possibly serve as an option for PGLs, in particular in metastatic disease (see chapter 4.6.3).

4.9 Other Focal Therapies

In selected paediatric patients with metastatic PGL, focal treatment of individual metastatic lesions may be considered as part of a multimodal, individualized approach, particularly when the number of lesions is limited, or when systemic disease control is inadequate. The choice of focal therapy depends on factors such as tumour location, patient age, overall clinical condition, and the expertise available within the treating centre.
Therapeutic options may include surgical resection, thermal ablation techniques (e.g. radiofrequency ablation, cryoablation), or, in specific anatomical settings, chemoembolization. These procedures may be used iteratively and are generally aimed at prolonging local disease control, alleviating symptoms, and delaying the need for systemic therapy.
The impact of these interventions on long-term outcomes in children with PGL remains undefined, and decisions should be guided by MDT discussion.
[Level V; Grade C]

4.10 Palliative Therapy

All therapeutic interventions for metastatic PGL – including systemic therapies such as chemotherapy, PRRT, and targeted therapies – are considered palliative in nature, as curative treatment is not achievable in these patients. The goal of therapy in this setting is to control disease progression, manage catecholamine-related symptoms, and maintain quality of life over the long term.

In paediatric patients with advanced, unresectable, or slowly progressing metastatic PGL, a chronic disease management approach is essential. While cure is not the goal, management should focus on symptom control, preservation of quality of life, and prevention of complications related to tumour progression or catecholamine excess.

However, given the often indolent course of metastatic PGL, treatment may be required over many years and must remain flexible and adaptive to disease dynamics. (11)

Therapeutic strategies - including iterative focal therapies, PRRT, [131I]I-MIBG, targeted agents, or carefully selected systemic therapies - may be administered sequentially or intermittently, depending on tumour behaviour, symptom burden, and patient tolerance. Management should be individualized and coordinated within a MDT, ideally involving palliative care specialists, to ensure holistic, patient-centred support.

[Level V; Grade A]

4.11 Treatment of Relapse

Relapse in paediatric PGL requires a systematic re-evaluation of disease extent and treatment options, with the primary objective being complete surgical resection whenever feasible. Given the indolent nature of many PGLs, recurrent disease may remain localized or oligometastatic, allowing for curative-intent surgery in select cases.

The first step in managing relapsed PGL is a comprehensive reassessment through:

- Biochemical testing to confirm recurrent catecholamine secretion.
- Imaging with local MRI and PET/CT (e.g., SSTR-directed PET/CT or [18F]F-DOPA PET/CT) to determine the extent of recurrence and rule out distant metastases.
- MDT board discussion to evaluate surgical feasibility based on tumour location, prior surgical interventions, and the patient's overall condition.

Whenever possible, new complete surgical resection, even in several sites, remains the preferred approach, as it offers the highest likelihood of long-term disease control. For patients with multifocal or bilateral recurrent disease, cortical-sparing adrenalectomy may be considered in hereditary cases to preserve adrenal function.

If surgery is not an option, treatment aligns with first-line recommendations, tailored to the extent and molecular profile of the disease.

The treatment of relapse in paediatric PGL follows first-line management principles, with surgical resection prioritized whenever feasible. For unresectable or metastatic cases, treatment

should be individualized based on tumour biology, molecular profile, and prior treatments, ideally within specialized centres or clinical trials.

[Level V; Grade B]

5. Assessments

Assessment during treatment and in the immediate post-operative period is essential to monitor for complications, biochemical resolution, and disease progression. Evaluations should be conducted at defined intervals to guide clinical decision-making and optimize patient outcomes.

5.1.1 Early Postoperative Biochemical Assessment

The success of surgical intervention is best evaluated through biochemical resolution of catecholamine excess. (11, 36, 138)

- Plasma-free or urinary (nor)metanephrines should be measured 2–8 weeks postoperatively to assess for biochemical remission.
- Plasma-3-Methoxytyramine levels should be checked in *SDHB*-mutated patients, as persistent elevation may indicate residual or metastatic disease.
- Serum chromogranin A may be considered in patients with non-functional tumours, but only if elevated prior to surgery, as its diagnostic utility is limited and postoperative interpretation is only meaningful in that context.

(11, 36, 138) *[Level V; Grade A]*

Persistent elevation of biochemical markers post-surgery necessitates imaging follow-up to exclude residual or metastatic disease. *[Level V; Grade A]*

5.1.2 Imaging Assessment Post-Surgery

Postoperative imaging is guided by biochemical results and initial tumour characteristics. (11)

- MRI or CT (preferably within 3 months post-surgery) in patients with incomplete resection, biochemical persistence, or non-functional tumours. (11, 36)
- Functional PET/CT imaging (SSTR-directed PET/CT or [18F]F-DOPA PET/CT) should be performed in cases where residual or metastatic disease is suspected.

[Level V; Grade B]

5.1.3 Ongoing Treatment Assessment for Non-Surgical Cases

For patients receiving systemic therapy (PRRT, TKIs, or chemotherapy), assessment includes:

- Regular biochemical testing every 3–6 months to monitor for tumour response.
- Cross-sectional imaging every 6–12 months depending on disease status and treatment response.
- Monitoring of systemic therapy toxicities, including renal function in PRRT-treated patients, thyroid and cardiovascular parameters in TKI-treated patients.

Comprehensive assessment during treatment and post-operatively is critical for early detection of complications, confirmation of biochemical remission, and monitoring of disease recurrence or progression. Biochemical and imaging-based evaluations should be tailored to individual risk factors and molecular profiles.

[Level IV; Grade A]

6. Follow-up

Long-term follow-up is essential for early detection of recurrent or new primary tumours, monitoring endocrine and metabolic complications, and preserving quality of life in paediatric patients with PGL. (8, 11, 139)Given the high recurrence risk and the frequent association with hereditary cancer predisposition syndromes, surveillance should be structured, multidisciplinary, and risk-adapted.

Follow-up should also account for the possibility of additional neoplasms arising within the context of underlying genetic syndromes (e.g., VHL, MEN2, NF1) or, more rarely, as a result of previous systemic or radiotherapeutic treatments. Therefore, surveillance strategies should be personalized based on to the individual's germline pathogenic variant, clinical history, and risk profile. While tumour-specific screening protocols exist for many syndromes, some genetic variants lack clearly defined follow-up strategies, particularly in paediatric patients. *[Level V; Grade A]*

For detailed guidance on gene-specific surveillance, clinicians should refer to the 2024 international paediatric PGL consensus statement, which outlines recommendations for follow-up across various genetic backgrounds and complements the broader management framework presented in this ESCP. (11) In addition, the most recent guidelines should be considered. *[Level V; Grade A]*

6.1.1 General Principles of Follow-Up

Lifelong surveillance is mandatory, particularly for patients with hereditary PGL syndromes (e.g., *VHL*, *SDHB* pathogenic variants), as they remain at high risk for new primary tumours. (6, 8, 9, 11, 98)

- Follow-up intervals should be individualized based on genetic status, initial tumour characteristics, and surgical outcomes.
- Multidisciplinary follow-up care, including paediatric oncologists, endocrinologists, cardiologists, and psychologists, ensures comprehensive patient support.

(Table 4) *[Level V; Grade A]*

Table 4. Recommended Surveillance Intervals

Measure	**First 5 years post-treatment**	**Beyond 5 years**
Biochemistry (metanephrine ± 3-methoxytyramine)	Every 6–12 months	Every 1–2 years, tailored to risk
MRI	Baseline at 6–12 months post-op, then every 1–3 years	Every 1–3 years, tailored to risk
Functional imaging	As indicated by abnormal biochemistry or symptoms	As indicated

6.1.2 Biochemical Monitoring

Regular plasma-free or urinary (nor)metanephrines should be assessed to detect biochemical recurrence. (11)

- Every 6 to 12 months in the first 5 years postoperatively, with shorter intervals (e.g., 6 months) considered for high-risk patients such as those with *SDHB* pathogenic variants
- Annually thereafter, if no evidence of disease is detected
- Plasma-3-Methoxytyramine levels should be included in follow-up for patients with initial noradrenergic biochemical profiles, including but not limited to those with *SDHB*-mutations, as a marker for tumour recurrence

[Level IV-V; Grade B]

Persistent or rising catecholamine markers should prompt early imaging and multidisciplinary evaluation. *[Level V; Grade A]*

6.1.3 Imaging Surveillance

Long-term imaging surveillance is essential for the early detection of recurrent or new tumours, particularly in patients with hereditary PGL, high-risk molecular profiles, or prior incomplete resections. The timing and modality of imaging should be tailored to the genotype, biochemical course, and initial disease characteristics, as outlined in Section 5.1.2. *[Level V; Grade B]*

For patients with biochemical normalization and no high-risk features:

- Abdominal (or focal) MRI (preferred) or CT should be performed at 6 to 12 months postoperatively to establish a radiological baseline, unless already done earlier as part of postoperative assessment.
- Subsequent imaging can be considered annually or every 2–3 years, depending on the tumour's genetic background (e.g., slow-growing *SDHx*-related tumours), biochemical profile, clinical context, and MDT decision. More frequent imaging may be appropriate in certain high-risk or hereditary PGL cases. Given the limited paediatric-specific data, surveillance strategies should be individualized.

[Level V; Grade B]

SSTR-directed PET/CT or [18F]F-DOPA PET/CT should be used selectively in patients with suspicion of recurrence, high-risk genetic pathogenic variants, or inconclusive anatomical imaging. *[Level V; Grade B]*

In *SDHB* pathogenic variant carriers, whole-body MRI may be preferred due to the higher metastatic risk and potential skeletal involvement. *[Level V; Grade B]*

6.1.4 Endocrine and Metabolic Follow-Up

Patients with bilateral adrenalectomy require lifelong adrenal hormone replacement with regular ACTH and cortisol monitoring.

Thyroid and parathyroid function should be assessed in *MEN2*-related PGL, given the risk of associated endocrine neoplasms.

Annual glucose and metabolic assessments are recommended to evaluate long-term complications of catecholamine excess or surgical intervention.

[Level V; Grade B]

6.1.5 Cardiovascular Follow-Up

Annual blood pressure monitoring to detect residual or secondary hypertension.

Echocardiography every 2–3 years in patients with a history of catecholamine-induced cardiomyopathy.

Holter monitoring in patients with prior arrhythmias or those receiving long-term systemic therapies (e.g., TKIs).

[Level V; Grade A]

6.1.6 Psychosocial and Genetic Counselling

Psychological support and counselling should be available for patients experiencing chronic anxiety, PTSD, or coping difficulties after treatment. (11)

[Level V; Grade A]

Genetic counselling and family screening are critical for first-degree relatives of pathogenic variant carriers to determine their need for surveillance.

[Level V; Grade A]

Follow-up care for paediatric PGL should be lifelong and risk-adapted, integrating biochemical, imaging, endocrine, cardiovascular, and psychosocial assessments. A multidisciplinary, structured approach ensures early detection of recurrence and long-term health optimization, particularly in hereditary cases requiring ongoing surveillance.

7. Transition from Paediatric to Adult Care

Given the lifelong risk of recurrence, new primary tumours, and long-term complications associated with PGL, a structured transition from paediatric to adult care is essential for ensuring continuity of surveillance and optimal disease management. Many paediatric patients, particularly those with hereditary syndromes (e.g., VHL, *SDHB* pathogenic variants, MEN2,

NF1), will require lifelong biochemical and imaging follow-up, making a well-coordinated transition plan critical. (11)

Initiation of transition discussions should begin in early adolescence (typically by age 16 years) to prepare the patient and caregivers for the shift in care responsibility. Comprehensive transition planning should involve a common MDT, including paediatric and adult endocrinologists, oncologists, genetic counsellors, and psychologists, to address medical, psychological, and lifestyle considerations. Personalized follow-up schedules should be developed based on individual risk profiles, genetic status, and previous treatment history to ensure seamless continuity of biochemical and imaging surveillance. Patient education and self-management skills should be emphasized to empower young adults to actively participate in their care, understand their genetic risks, and recognize early symptoms of recurrence. Coordination between paediatric and adult healthcare teams should be formally structured, with at least one transition consultation involving both providers to facilitate information exchange and minimize the risk of care gaps.

A structured and proactive transition process is critical for paediatric PGL patients to maintain long-term surveillance, prevent loss to follow-up, and optimize lifelong disease management. The transition should be gradual, patient-centred, and multidisciplinary, ensuring that young adults are well-prepared to manage their condition in the adult healthcare setting.

[Level V; Grade B]

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APPENDIX 1

Tumour-Node-Metastasis (TNM) staging (8th edition)

Tumour (pT)	
TX	primary tumour cannot be assessed
T1	tumour < 5 cm in greatest dimension, no extra-adrenal invasion
T2	tumour ≥ 5 cm or sympathetic paraganglioma of any size, no extra-tumoral/extra-adrenal invasion
T3:	tumour any size with invasion into surrounding organs/tissues (e.g., liver, pancreas, spleen, kidneys)
Regional lymph nodes (N)	
NX	regional lymph nodes cannot be assessed
N0	no lymph node metastasis
N1	regional lymph node metastasis
Distant metastases (M)	
M0	no distant metastasis
M1a	distant metastasis to only bone
M1b	distant metastasis to only distant lymph nodes/liver or lung
M1c	distant metastasis to bone and multiple other sites
Stage groups	
Stage 1	T1, N0, M0
Stage 2	T2, N0, M0
Stage 3	T1, N1, M0 or T2, N1, M0 or T3, any N, M0
Stage 4	any T, any N, M1

(78)

APPENDIX 2

Age- and sex-specific upper reference limits for plasma free normetanephrine, metanephrine, and 3-methoxytyramine, as presented in Casey et al. (11), derived from healthy volunteers in Peitzsch et al. (58)

Reference Population	Upper reference limits (pmol/l) for plasma free metabolites		
	Normetanephrine	Metanephrine	Methoxytyramine
3 - <6 years			
Girls	632	527	203
Boys	1.362	517	157
6 - <13 years			
Girls	1.242	724	165
Boys	897	537	170
13 - <18 years			
Girls	754	374	174
Boys	732	355	174

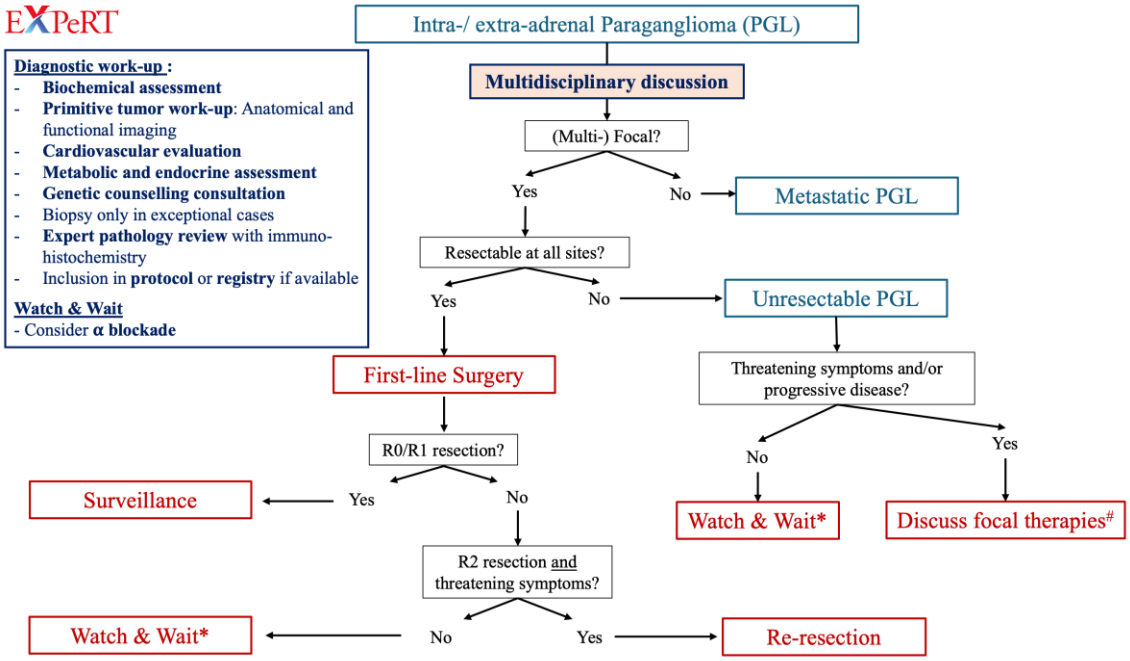
Age-specific upper reference limits for spot urine metanephrines, as presented in Casey et al. (11), based on the reference population in the study of Pussard E et al. (140)

Reference Population	Upper reference limits (µg/gr creatinine) for spot urine metabolites	
	Normetanephrine	Metanephrine
2 - < 5 years	738	371
5 - <10 years	465	310
10 - <15 years	339	228
15 - <20 years	275	126

APPENDIX 3

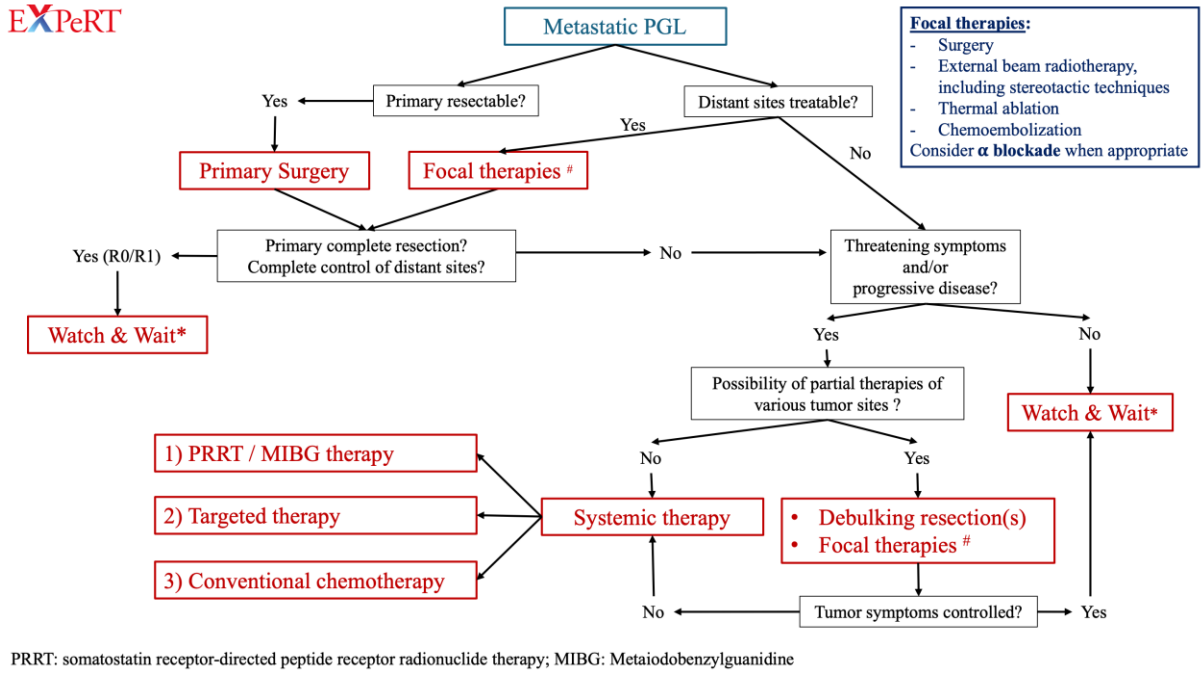
Flowchart of recommended diagnostic and therapeutic approach for localized or resectable paediatric adrenal and extra-adrenal paraganglioma (PGL).

This diagram outlines key decision points including assessment of focality, resectability, surgical management, and the role of surveillance, re-resection, or focal therapies following initial surgery.



Flowchart of recommended management of metastatic or unresectable paediatric adrenal and extra-adrenal paraganglioma (PGL).

The diagram illustrates treatment pathways for metastatic disease, including decision points for surgery, focal therapies, debulking, systemic therapies (PRRT, MIBG therapy, targeted therapy, chemotherapy), and indications for surveillance (watch and wait).



PRRT: somatostatin receptor-directed peptide receptor radionuclide therapy; MIBG: Metaiodobenzylguanidine

Abbreviations: PRRT = somatostatin receptor-directed peptide receptor radionuclide therapy; MIBG = metaiodobenzylguanidine.