PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

ENDOCRINE

PHEOCHROMOCYTOMAS/PARAGANGLIOMAS

Endocrine Site Group – Pheochromocytomas/Paragangliomas

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1. INTRODUCTION & SUMMARY OF RECOMMENDATIONS

During the last decade there have been revolutionary breakthroughs in understanding the biology of pheochromocytomas (PCCs) and extra-adrenal paragangliomas (PGLs). It is now recognized that at least 30% of these tumors are hereditary, caused by germline mutations of several genes. Hereditary PCCs and extra-adrenal PGLs arising in patients with different genotypes have characteristic distributions and biochemical profiles and different likelihoods of metastasis. In addition, a widening spectrum of associated tumors — including gastrointestinal stromal tumors, renal cell carcinomas, and pituitary adenomas — is associated with newly discovered hereditary tumor syndromes. Discoveries of new susceptibility genes and genotype-phenotype correlations have led to the realization that appropriate patient care requires a complete integration of clinical, genetic, biochemical, imaging, and pathology findings. There is a corresponding need for updates in clinical practice to incorporate these recent discoveries. We therefore propose a new synoptic reporting approach for PCCs and extra-adrenal PGLs that will provide clear and uniform information to pathologists and clinicians, in order to advance the diagnosis of these neoplasms and optimize patient care.

SCOPE OF GUIDELINES

Beyond the differential diagnosis, clinico-pathologic correlations play an important role in identifying clues to hereditary disease and alerting clinicians to possible associated lesions and their potential significance. The proposed checklist below aims to provide uniform and complete data to allow thorough evaluation of PCCs and extra-adrenal PGLs. This checklist will guide in the development of standardized reporting. It does not include the detailed information required to reach the diagnosis of PCC or extra-adrenal PGL; that is provided elsewhere[2-6]. A novel component of the checklist is a formatted clinicopathologic correlation.

i. Access to a multidisciplinary endocrine cancer team

a. Management of PCCs and PGLs is the responsibility of a specialized multidisciplinary team, membership of which will normally be comprised of an endocrinologist, pathologist, surgeon, clinical geneticist, and radiation oncologist, with support from a specialist nurse, all with expertise and interest in the management of endocrine cancers.
b. Patients will normally be seen by one or more members of the multidisciplinary team; a combined clinic is recommended, and all members of the multidisciplinary team should maintain continued professional development on an on-going basis.

ii. Patient focus

a. Patients should be offered full informed consent about their condition and their treatment.
b. Patients should have continued access to a multidisciplinary team for guidance, support and follow up.

iii. Surgery

a. The surgeon should have training and expertise in the management of endocrine cancer and be a member of the multidisciplinary team.

iv. Pathology

a. Pathologists dealing with endocrine tumors should have expertise and interest in adrenomedullary cytology, histopathology, and molecular biology of adrenal tumors.
b. All patients should be staged by clinical and pathological TNM staging. Pathology reporting should be synoptic and comprehensive.
c. Risk group assignment. Patients will be followed according to their risk, which is based on their genotype, radiologic findings and surgical pathology.

v. Aims of Treatment

The aims of treatment are the removal of all tumour (when indicated), the elimination of clinical, radiological or biochemical evidence or recurrence and minimization of unwanted side-effects.

vi. Summary of management of differentiated adrenomedullary pheochromocytomas/paragangliomas

a. All new patients should be seen by a member of the multidisciplinary team and treatments plans should be discussed and endorsed by the multidisciplinary team. Complex cases should be reviewed at multidisciplinary tumour boards prior to any intervention.
b. Fine needle aspiration cytology should not be used in the planning of surgery.
c. Following bilateral adrenal surgical removal, patients will require adrenocortical hormone therapy at a dose sufficient to replace normal production. Blood and urinary hormone levels can be used to guide replacement dosing.

vii. Follow-up of adrenomedullary pheochromocytomas/paragangliomas

a. Follow-up should be life-long in patients with both sporadic and germline disease. In patients with germline disease additional manifestations outside of the adrenals may require further investigations and/or treatment.
b. Surveillance for recurrence of disease is essential and is based on annual clinical examination, annual measurement of urine catecholamines and metanephrines (as well as chromogranin A in selected cases), and annual diagnostic imaging studies where indicated.

viii. Medullary thyroid cancer

The initial evaluation of suspected medullary thyroid cancer, which is an important component of the familial endocrine neoplasia syndromes type 2 (MEN-2), is covered in the PMH Thyroid Cancer Treatment Guidelines.

2. PREVENTION

Prevention is possible when genetic and/or biochemical information can provide sensitive and specific information. In general, Mendelian genetics form the basis for gene-informed risk assessment and management for patients and their families. This is the true meaning of 21st century personalized medicine, yet it has not occurred with some specific exceptions.

About a third of pheochromocytomas/paragangliomas (PPGLs) are familial. The mode of transmission is autosomal dominant. Nevertheless, penetrance for PPGLs is often low and in some cases is still unknown. Moreover, with a very few exceptions, hereditary forms of PPGLs tend to be associated with a low risk of malignancy. In that context, current evidence does not support prophylactic adrenalectomies in individuals harbouring germline mutations that predispose to the development of pheochromocytomas. However, knowledge of the germline mutations underlying PPGLs is warranted for the purpose of tailoring treatment and follow up of the affected individual as well as that of the individuals at risk. For example, individuals with *SDHB* mutations harbour the highest risk of metastatic disease and affected individuals merit close surveillance.

In the next sections we will review the genetic basis of what causes familial PPGLs and how this relates to the different phenotypes, diagnosis, treatment, and follow up. It is clear though that during the following years more information will be available allowing for a more comprehensive approach.

3. GENETICS AND SCREENING

3.1 Genetics

The spectrum of the genetics that underlie pheochromocytomas and paragangliomas (PPGLs) has broadened during the last few years. In the context of familial disease several new germline mutations have been reported and at the moment there are 10 susceptibility genes that have been identified:

1. Rearranged During Transfection (*RET)*[7-9]
2. Von Hippel Lindau (*VHL)*[10,11]
3. Neurofibromatosis type 1 (*NF-1*)[12,13]
4. A subunit of the mitochondrial succinate dehydrogenase complex (*SDHA*)[14]
5. B subunit of the mitochondrial succinate dehydrogenase complex (*SDHB*)[15]
6. C subunit of the mitochondrial succinate dehydrogenase complex (*SDHC*)[16]
7. D subunit of the mitochondrial succinate dehydrogenase complex (*SDHD*)[17,18]
8. *SDHFA2*[19,20]
9. MYC-associated factor X (*MAX)*[21,22]
10. Transmembrane protein 127 (*TMEM127)*[23]

In sporadic disease there has been the recent description of new somatic mutations. First, gain-of-function mutation of the endothelial PAS domain protein 1 gene also known as *HIF2α* was found to be the underlying genetic defect of the polycythemia, paraganglioma/pheochromocytoma syndrome with or without somatostatinoma[24-26]. Second, mutations in *H-RAS* hot spot codons activating the RAS/RAF/ERK pathway where found in males with benign pheochromocytomas[27]. Additionally, 10% of sporadic PGL cases were found to be associated with mutations in *SDHB or SDHD*[28,29], mutations of the *VHL and RET* genes were found to be present in 14% of sporadic PPGLs, and mutations in *MAX* are found in almost 2% of sporadic PCCs [22,29,30].

Twenty five to approximately 33% of all the patients with PPGLs have germline mutations[31,32]. The risk of harbouring these mutations depends on the family history and the presence of phenotypic features suggestive of a familial syndrome. If there is a family history of PPGLs more than 90% of patients with PPGLs will have a germline mutation of *VHL, RET, SDHB, SDHC, SDHD* or *NF-1*. The risk is about 39% in apparently sporadic disease that is multiple and/or recurrent that percentage decreases to about 39%, and is reduced to approximately 12% in the context of single tumors[32].
Each of the most recently discovered mutations in *SDHFA2*, *MAX*, and *TMEM127* contribute to ≤ 2 % of PPGLs[20,22,33].

3.3 Screening

There are currently two methods of screening for familial pheochromocytomas or paragangliomas: genetic testing and biochemical studies.

3.3.1 Genetic testing

Recent molecular data suggest genotype-phenotype correlations in PGLs with respect to tumor distribution, catecholamine production and risk of metastasis[6,34-41]. Specific genotype-biochemical correlations highlight the importance of laboratory testing to characterize patterns of catecholamine excess. Since catecholamines (dopamine, norepinephrine, and epinephrine) are not continuously secreted in normal conditions, biochemical testing for the O-methylated metabolites of dopamine, norepinephrine and epinephrine (methoxytyramine, normetanephrine and metanephrine, respectively) in plasma and/or urine is superior to measurement of the parent catecholamines [34,39,40]. In terms of their biochemical profile, *SDH*x-related tumors are associated with dopamine and/or norepinephrine production, *VHL* and MAX-related tumors are associated with norepinephrine production, *RET* and *NF1*-related tumors are associated with epinephrine production, *TMEM*127-related tumors do not have preferential secretion of norepinephrine or epinephrine[6,22,33,34]. Tumors that are adrenal and bilateral with a predominantly adrenergic phenotype and presenting in individuals younger than 50 are more likely to be due to *RET* mutations. On the other hand, tumors that are unilateral in very young individuals with a predominantly noradrenergic profile are more likely to be due to *VHL* mutations. Moreover, the risk of malignancy is significantly higher in *SDHB*-related chromaffin cell tumors, which are usually observed in extra-adrenal locations and reach larger sizes with much lower tissue concentrations of catecholamines than other PGLs[34,36-39]. These data are of clinical significance and become essential in guiding genetic testing.

3.3.1. Biochemical screening

While PCCs and the majority of sympathetic PGLs are often associated with clinical symptoms, only a small percentage of parasympathetic PGLs are symptomatic. Many clinically silent PGLs, particularly of the sympathoadrenal type will produce metanephrines and/or methoxytyramine and therefore be amenable to biochemical testing[34,42]. However, parasympathetic paragangliomas often lack tyrosine hydroxylase, the enzyme required for catecholamine synthesis, and are therefore usually non-functional[6]. Rarely, PPGLs may also lack the capacity to synthesize norepinephrine due to lack of dopamine-β-hydroxylase[43]; these tumors produce dopamine and are difficult to diagnose because patients will usually be normotensive[44].

Similar to other neuroendocrine neoplasms, PCCs and extra-adrenal PGLs are also capable of producing and secreting other peptides that can cause clinical syndromes. Production of ACTH, β-endorphin, CRH, calcitonin gene-related peptide, VIP, GHRH, neuropeptide Y, peptide YY, IGF-1, galanin, adrenomedullin, serotonin, somatostatin and gastrin-like neuropeptide have been reported[2-6,45-49].

The most sensitive tests for screening seem to be plasma free metanephrines as well as urinary fractionated metanephrines measured by liquid chromatography with electrochemical detection (LCED)[50]. Specificity is higher with urinary total metanephrines than with plasma or urine catecholamines. When measuring plasma metanephrines the known physiologic sympathetic response to postural changes has to be taken into account and it is generally recommended that blood samples are taken with the patient in a supine position.

4. CLINICAL PRESENTATION AND CLINICAL DIAGNOSIS

4.1 Epidemiology

The incidence of pheochromocytomas/paragangliomas (PPGLs) is about 2 cases per million per year[51,52] with an almost even distribution among sexes[31,32,51,52]. The mean age of presentation of non-hereditary disease is 44 years while it is 24 years for cases associated with germline mutations[31]. Amongst ambulatory patients with hypertension the prevalence of pheochromocytomas is very low (0.1% to 0.6%)[53,54] but there is no data on the prevalence amongst patients with resistant hypertension.

Metastatic disease is not a rare event. In referral centres, which are obviously subject to a referral bias, up to 33% of PPGLs are metastatic[55].

4.2 Classification

PPGLs may be classified according to several different parameters:

1. Anatomic localization:
   a. Abdominal (adrenal or extra-adrenal)
   b. Thoracic
   c. Head and neck
2. Functionality:
   a. Predominantly adrenergic (epinephrine/metanephrines)
   b. Predominantly noradrenergic (noradrenaline/normetanephrine)
   c. Predominantly dopaminergic (dopamine/methoxytyramine)
   d. Mixed
3. Sporadic or Familial
4. Benign or malignant

4.3 Clinical Presentation

PPGLs can present as apparently sporadic disease or in the context of a family history and/or a phenotype suggestive of germline disease (Table 1). Age plays an important role in predicting the likelihood of inherited PPGLs syndromes. The younger an individual is at the time of presentation the more likely it is that their disease is hereditary[31,32]. In a large European series, patients older than 50 years who presented with an apparently sporadic pheochromocytoma/paraganglioma had an incidence of less than a 1.3% of *VHL*, *MEN2*, *SDHB*, or *SDHD* mutations and the percentage was reduced to cero in patients older than 60 years[31]. Nevertheless, as the mutational spectrum of the disease becomes wider is likely that older patients will be found to have germline mutations too. In addition to a younger age of diagnosis, the presence of paragangliomas and/or bilateral pheochromocytomas should alert to the possibility of familial disease[56,57].

Pheochromocytomas and sympathetic paragangliomas are usually hormonally active whereas parasympathetic paragangliomas rarely exhibit hormonal hypersecretion.

Symptoms of functional PPGLs may be acute in the form of "spells" and/or chronic. Spell related symptoms include: headache, palpitations, diaphoresis, hypertension, dyspnea, anxiety, pallor, chest pain, epigastric pain, tremor, weakness, and fatigue after the spell[58]. Chronic symptoms include hypertension, orthostatic changes, hypertensive retinopathy, tremor, weight loss, tremor, hyperglycemia, congestive heart failure, constipation, and fever. Not all patients with functional tumors are hypertensive and blood pressure does not correlate with circulating levels of catecholamines[59].

Pheochromocytomas in which the biochemical phenotype is predominantly adrenergic such as in the context of Multiple Endocrine Neoplasia Type 2 (MEN2), are more frequently symptomatic and manifest more often with paroxysmal hypertension and typical spells of diaphoresis, headaches, palpitations, and anxiety when compared to tumors with a noradrenergic profile such in the context of Von Hippel Lindau (VHL)[60]. In MEN2 patients, pheochromocytomas express phenylethanolamine n-methyltransferase (PNMT) whereas those in VHL patients have a very low expression of this enzyme. The former also express more tyrosine hydroxylase (TH) and synthetize more catecholamines, nevertheless, plasma concentrations of total catecholamines are lower due to less secretion[60].

Most studies report a risk of malignancy of less than 1% in patients with MEN2 (Table 1), but in one particular study up to 4% of patients had metastatic disease[61]. In VHL the risk of malignancy has generally been reported as being very low. However, there is one kindred from German descent that has shown a 20% incidence of metastatic disease[62]. Of all the known familial forms of PPGLs, familial PPGLs type 4 is the one that is associated with the highest risk of malignancy. In general about 30% of malignant PPGLs are due to *SDHB* mutations, with paragangliomas having a higher risk of being malignant [63]. Additionally, amongst patients who are *SDHB* mutation carriers the incidence of malignant PPGLs has been reported to be as high as 71.4%[57]. About 15% of sporadic PPGLs are malignant[57]. PPGLs most frequently metastasize to the bone followed in descending order by lymph nodes, lung, liver and peritoneum[64].

Table 1. Genotype-phenotype relations of familial syndromes associated with PPGLs				
Syndrome	Mutated gene and pattern of inheritance	Biochemical phenotype of functional tumors	Clinical phenotype	Frequency of malignancy
MEN2a	*RET* AD*	Predominantly adrenergic[60,65,66]	Usually bilateral pheochromocytomas [65,67,68]. Primary hyperparathyroidism, medullary thyroid carcinoma.	≤1%[55,57,65,68,69]
MEN2b			Usually bilateral pheochromocytomas[57,68,69]. Medullary thyroid carcinoma, marphanoid habitus, mucosal neuromas, ganglioneuromatosis of the gastrointestinal tract, skeletal abnormalities.	
Neurofibromatosis type 1	*NF-1* AD*	Predominantly adrenergic[66]	Usually unilateral pheochromocytomas[57] or rarely sympathetic paragangliomas[70] *Cafe au lait* macules, neurofibromas, freckling in the axillary of inguinal regions, optic glioma, iris hamartomas, sphenoid dysplasia or thinning of long bone cortex[1].	<10%[57,70]
Type 2 von Hippel Lindau	*VHL* AD	Predominantly[60,62] noradrenergic	Usually pheochromocytomas that may be unilateral or bilateral[56,62] Sympathetic and parasympathethic paragangliomas may occur[32] CNS hemangioblastomas, renal cell carcinoma, pancreatic NET, endolymphatic sac tumors, benign cysts (kidneys, pancreas, epididymis, ovaries)[71]	<5%[32,55,56,71]
Familial PGL1	*SDHD* AD-Paternal (maternal imprinting)	Noradrenergic and dopaminergic[66]	Usually head and neck paragangliomas and less frequently pheochromocytomas or parasympathetic paragangliomas[72,73] Renal cell carcinomas[73], possibly pituitary tumors[74]	<5%[32,73]
Familial PGL2	*SDHAF2* AD-Paternal (maternal imprinting)	Generally non-functional tumors	Head and neck paragangliomas[19]	Close to cero[20,75]
Familial PGL3	*SDHC* AD	Frequently non-functional but may be noradrenergic[29] or dopaminergic	Most frequently head and neck paragangliomas[29] and exceptionally sympathetic paragangliomas[76] Possibly pituitary tumors[77]	Close to cero[29]
Familial PGL4	*SDHB* AD	Noradrenergic and dopaminergic[66]	Usually sympathetic paragangliomas and less frequently pheochromocytomas[57,63] Renal cell carcinoma[73], papillary thyroid cancer[72]	20%-35%[32,57,63,64,73]
*AD: autosomal dominant This table was adapted from Gomez K & Ezzat S. Clinical Manifestations of Endocrine Diseases. In: Asa SL, Mete O, editors. Endocrine Pathology. Cambridge University Press. In Press				

4.3 Diagnosis

A. Biochemical

The most sensitive tests for the biochemical diagnosis of PPGLs are plasma free metanephrines and urinary fractionated metanephrines measured by liquid chromatography[50]. At our institution we routinely measure urine metanephrines as well as urine catecholamines. Elevation of urine metanephrines >2.5 the upper limit of normal is always suspicious of a true positive result and merits appropriate follow up[78].

There are several drugs and conditions that may be associated with false positive results. In general most drugs do not directly interfere with the assay but rather transiently affect endogenous catecholamines and for that reason they should not be discontinued before testing. Nevertheless, knowledge of their possible effects is fundamental for appropriate interpretation of data:

1. Phenoxybenzamine and tricyclic antidepressants may result in elevations of urine and plasma normetanephrine and norepinephrine when using liquid chromatography with electrochemical detection (LCED)[79].
2. Selective α-1 blockers may lead to elevated urine norepinephrine (LCED) [79].
3. Beta-blockers may increase plasma and urinary metanephrines as well as urinary norepinephrine, normetanephrine and epinephrine (LCED) [78,79].
4. Calcium channel blockers may increase plasma and urinary norepinephrine as well as urinary epinephrine (LCED) [79].
5. Sympathomimetics may cause elevations of urinary normetanephrine or metanephrines (LCED)[79].
6. Carbidopa-levodopa may selectively increase the levels of urine dopamine [78].
7. Acetaminophen has a similar retention time with that of normetanephrine and so it can lead to elevations of plasma normetanephrine when using LCED[80].
8. Buspirone is likely to have a metabolite that causes a chromatographic artefact resulting in increased urine metanephrines when using LCED [81].
9. Tricyclic antidepressants, labetalol, sotalol, and over the counter decongestants may lead to spectral interference so that when using spectrophotometry (superseded now by LC) one might expect falsely elevated urinary total metanephrines[82].
10. Major physical stress leading to increased adrenergic activity (sleep apnea, hypoglycaemia, infections, stroke, severe congestive heart failure, myocardial infarction)[82,83].

B. Localization of pheochromocytomas/paragangliomas

Once biochemical diagnosis has been established the next step is localization of disease. Imaging may be done in the absence of biochemical evidence of disease in selected cases where there is a strong suspicion of disease that is non-functional.

Anatomic Localization of Disease with Computed Tomography (CT) and Magnetic Resonance (MR)

CT and MRI are generally used for initial localization of PPGLs. These imaging modalities have a high sensitivity although they are not very specific[84]. The adrenals are usually imagined with and without contrast. Intravenous CT contrast agents are not contraindicated in patients with suspected PPGLs and pharmacologic blockage is not routine practice prior to these imaging examinations[85,86].

In the context of pheochromocytomas radiologic findings are helpful but may be overlapping with other conditions. The previously described classic MR imaging finding of "light bulb" bright signal intensity on T2 weighted images has variable and low sensitivity[87,88]. Recently a small percentage of pheochromocytomas have exhibited CT attenuation and absolute or relative washout characteristics overlapping those of adenomas[89,90].

Functional Imaging with Tumor Scintigraphy or Positron Emission Tomography (PET).

As with genotype-biochemical profile correlations of PGLs, the functional status of a PGL has an impact on imaging modalities that are used to localize these lesions[35]. ^{123}I-metaiodobenzylguanidine scintigraphy (^{123}I-MIBG) and 18F-6-fluorodopamine (^{18}F-FDA) or 18F-6-fluorodihydroxphenylalanine (^{18}F-FDOPA) PET, are superior to other functional imaging modalities for detecting PCCs[35,91]. In contrast, 18F-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET is more useful than other modalities for diagnostic localization of *SDHB*-driven metastatic PGLs[35,91,92], whereas ^{18}F-DOPA PET has been reported to be the most effective functional imaging modality for localization of *SDHx*-related head and neck PGLs[93]. Recently, it has been shown that ^{18}F-FDOPA-PET is most useful for the detection of head and neck PGLs and neuroendocrine neoplasms arising in patients with VHL syndrome[94]. When available, the integration of functional imaging data is of clinical interest and will ascertain the completeness of the synoptic report.

At our institution we are working to provide personalized management of PPGLs. In the near future we hope that PET with various agents will become available. PET is superior to MIBG scintigraphy for localization of PPGLs especially if familial, metastatic or extra-adrenal[95]. For the moment we are able to offer ^{131}I-MIBG scanning and ^{18}F-FDG PET; the latter has been suggested to be the imaging modality of choice for metastatic disease[64].

5. DIAGNOSTIC SURGICAL PATHOLOGY

5.1 Classification of pheochromocytomas/paragangliomas

A. Anatomic location

Anatomic location impacts the terminology used for these tumors. In the presence of metastatic disease, the term "metastatic" should be used. The term "composite" is used when a tumor combines features of paragangliomas (PGL) or pheochromocytomas (PCC) with those of malignant peripheral nerve sheath tumor, ganglioneuroma, ganglioneuroblastoma and neuroblastoma. Comprehensive data related to neuroblastic and related components should be reported using the designated synoptic checklist[96]. The histological classification generated from the recommendations of the 2004 World Health Organization Classification of Tumors of Endocrine Organs[3] is listed below, however for simplicity; the format proposed is shortened to allow a practical approach for synoptic reporting and accurate communication.

Classification of Pheochromocytomas and Extra-Adrenal Paragangliomas

Adrenal gland

___Pheochromocytoma
___Metastatic pheochromocytoma
___Composite pheochromocytoma (specify components): _____

Extra-adrenal localizations

___Carotid body paraganglioma
___Jugulotympanic paraganglioma
___Vagal paraganglioma
___Laryngeal paraganglioma
___Aortico-pulmonary paraganglioma
___Gangliocytic paraganglioma
___Cauda equina paraganglioma
___Orbital paraganglioma
___Nasopharyngeal paraganglioma
___Extra-adrenal sympathetic paraganglioma
___Superior and inferior paraaortic paraganglioma
___Urinary bladder paraganglioma
___Intrathoracic and cervical paravertebral paraganglioma
___Metastatic paraganglioma
___Composite paraganglioma (specify site and components):
___Others (specify): _____

B. Associated Lesions

It is widely accepted that adrenal medullary hyperplasia is a precursor lesion of pheochromocytomas arising in MEN 2 syndrome and is characterized by a nodular and/or diffuse enlargement of the adrenal medulla[2-6]. Since other predisposing genetic syndromes are not associated with adrenal medullary

hyperplasia, the determination of underlying adrenal medullary hyperplasia is one of the clinical responsibilities of pathologists examining adrenal glands. When examining diffuse hyperplasia, it is important to remember that medulla is normally present only in the head and body, but not in the tail of the gland with only minimal extension into the alae[2,4,5]. Although it is sometimes hard to define the tail of the adrenal due to distortion of the gland by tumor, the presence of adrenal medullary tissue in the tail qualifies as adrenal medullary hyperplasia. In general, medulla should not represent more than one-third of the gland thickness, with cortex on each side comprising the other two thirds. The distinction of PCC from nodular adrenal medullary hyperplasia is arbitrary since even microscopic nodules observed in the setting of MEN 2 syndrome represent clonal proliferations; therefore they are indeed neoplastic lesions[2,5]. However, nodules less than 1 cm can be practically considered to represent hyperplasia[4], provided that they grossly and microscopically resemble the rest of the medulla. It should be remembered that adrenal medullary nodules and PCCs can occur in MEN 2 adrenals without an obvious background of diffuse hyperplasia. The adrenal adjacent to an apparently sporadic pheochromocytoma should therefore be "breadloafed" and carefully examined for small nodules. Of note, a 61-year-old man with an *SDHB* mutation was found to have bilateral adrenal medullary hyperplasia characterized by an increased cortex to medulla ratio of 1:1 in both glands[97].

5.2 Pathology checklist summary

Select a Single Response Unless Otherwise Indicated

† Data elements marked with this are not required. They may be important but are not yet validated or regularly used in a patient management.

Specimen (select all that apply) (note A)
___Adrenalectomy
___Right
___Left
___Bilateral
___Extra-adrenal excision (specify): _____
___Other (specify): _____
___Not specified

Clinical and Biochemical Features (select all that apply) (note B)
___Biochemically Functioning
__Metanephrine and/or adrenaline
__Normetanephrine and/or noradrenaline
__Methoxytyramine and/or dopamine
__Other (specify): _____
___Biochemically silent
___Biochemical analysis not performed
___Family history (specify): _____

†Tumor Scintigraphy or PET (select all that apply) (note C)
___123I-metaiodobenzylguanidine scintigraphy
___18F-6-fluorodopamine PET
___18F-6-fluorodihydroxphenylalanine PET
___18F-fluorodeoxyglucose PET
___Other (specify): _____

Tumor Location and Size (from imaging) (note D)
Anatomic location (specify): _____
Greatest dimension: ___ cm
†Additional dimensions: ___ x ___ cm
Second dominant tumor if multifocal
___x ____x ____cm
†Additional dimensions if more than 2 foci: _____
___Cannot be determined

†Received:
†___Fresh
†___In formalin
†Fixation time: _____
†___Other (specify): _____

†Specimen Integrity
†___Intact
†___Fragmented

Specimen Size
___x ____x ____cm
†Additional dimensions: _____

†Specimen Weight
†___grams

Tumor Focality
__Unifocal or
__Multifocal (specify #): _____

Tumor Size
Dominant tumor
___x ____x ____cm
Second dominant tumor if multifocal
___x ____x ____cm
†Additional dimensions if more than 2 foci: _____

Histologic Features (Note E)
Growth pattern (select all that apply)
- ___Nested (alveolar, zellballen) pattern
- ___Trabecular pattern
- ___Diffuse (solid) pattern
- ___Expanded large confluent nests

___Other (specify): _____

Composite tumor elements (select all that apply)
___Absent
___Present (select all that apply):
___Neuroblastoma
Specify extent (%):
Degree of differentiation of the neuroblastic component (select all that apply)
___Undifferentiated
___Poorly differentiated
___Differentiating
___Cannot be assessed
___Ganglioneuroblastoma
Specify extent (%):
Subtypes:
___Nodular subtype
Specify number of nodules: _____
Specify the degree of differentiation for each neuroblastic nodule: _____
___Intermixed subtype
___Ganglioneuroma
Specify extent (%):
___Malignant peripheral nerve sheath tumor
Specify extent (%):
___Neuroblastic tumor, NOS
Specify extent (%):
___Other (specify):

Cytologic variants of Chromaffin and/or Chief cells (select all that apply)
___Epithelioid
___Clear cell
___Spindle cell
___Lipid cell change
___Oncocytic change

Necrosis
___Not identified
___Present, focal (small microscopic foci or single cell necrosis)
___Present, extensive (central, expansive or "comedo" necrosis)

Mitotic rate (select all that apply)
††Based upon counting 50 high-power fields (HPF: 40x objective) and in the area of highest mitotic activity, and reported as number of mitoses per 10 HPF)
_____Specify mitoses per 10 HPF: _____
_____Atypical mitoses
_____Cannot be determined

Additional Features
___Hyaline globules

___Amyloid deposition
___Neuromelanin deposition
___Myxoid and/or hyaline stroma
___Degeneration (specify): _____

Encapsulation and Invasion (note F)
___Thick capsule
___No capsule
___Cannot be determined

Invasive growth (select all apply)
Tumor capsule invasion (transcapsular)
___Present
Specify the extent of invasion (number of foci): _____
___Not identified
___Indeterminate

Adrenal capsule invasion (transcapsular)
___Present
Specify the extent of invasion (number of foci): _____
___Not identified
___Indeterminate

Local invasion into surrounding tissues
___Present
Specify tissues: _____
Specify extent (gross or microscopic): _____
___Not identified
___Indeterminate

Vascular invasion (intravascular tumor cells associated with thrombus)
Intracapsular
___Present
Specify the extent of invasion (number of vessels involved): _____
___Not identified
___Indeterminate
Beyond capsule
___Present
Specify the extent of invasion (number of vessels involved):
_____
___Not identified
___Indeterminate

Lymphatic invasion
___Present
___Not identified
___Indeterminate

Surgical margins
___Uninvolved

†Distance to closest margin: _____
___Involved
___Gross
___Microscopic
___Cannot be assessed
___Other (specify): _____

Metastases (note G)
___Lymph node metastases
___Present
___Not identified
___Indeterminate
___Number of lymph nodes examined
___Number of metastatic lymph nodes
Number of lymph nodes with macrometastases (>2 mm): ___
Number of lymph nodes with micrometastases (>0.2 mm to 2 mm and/or >200 cells): ___
Number of lymph nodes with isolated tumor cells (≤0.2 mm and ≤200 cells): ___

___Extranodal extension
___Present
___Focal (microscopic)
___Extensive
___Not identified
___Indeterminate

___Distant metastases (specify): _____

Immunohistochemistry (Check all positive or select all that apply) (note H)
___Chromogranin A
___Synaptophysin
___Tyrosine hydroxylase
___S100 protein (sustentacular cells)
___Loss of SDHB expression
___Loss of SDHA expression
MIB-1 (Ki-67) LI (percentage of positive tumor cells in area of highest nuclear labeling): __%
Others (specify):_____

Tumor Type (note I)
___Pheochromocytoma(s) specify site (s):_____
___Extra-adrenal paraganglioma(s) specify site(s):_____
___Composite pheochromocytoma (specify):_____
___Composite paraganglioma (specify site and components):_____
___Gangliocytic paraganglioma
___Metastatic pheochromocytoma, specify site: _____
___Metastatic paraganglioma, specify site: _____
___Other (specify):_____

Associated Lesions (note J)

___Adrenal medullary hyperplasia
___Current or past tumors in other organs (specify)

Clinicopathologic Correlation (Check all that apply)
___Evidence of hereditary disease
Clinical
Associated lesions (specify): _____
Biochemical profile (specify): _____
Pathological
___Multiple pheochromocytoma/paraganglioma
___Adrenal medullary hyperplasia
Immunohistochemistry (specify): _____

†Comment(s):_____

5.3 Explanatory notes

A: Anatomical Sites of Paraganglia

Paraganglia are neural crest-derived neuroendocrine organs that produce predominantly catecholamines[3,5,6]. Paraganglia are typically divided into two groups based on parasympathetic or sympathetic nervous system origin. Sympathetic paraganglia are also divided into two subgroups: the adrenal medulla, so-called "sympathoadrenal paraganglia" and extra-adrenal sympathetic paraganglia[2,4,5]. The anatomic site impacts the nomenclature of tumors arising from paraganglia; while tumors arising from the adrenal medulla are termed "pheochromocytomas (PCCs)", tumors arising from extra-adrenal locations are called "paragangliomas (PGLs)" regardless of their sympathetic or parasympathetic origins [2-6]. Furthermore, the anatomic site of a tumor predicts the risk of malignancy, since extra-adrenal paragangliomas exhibit a higher risk of malignancy[2-6,34,40,55,98].

B: Tumor Location, Size, Weight and Focality

The significance of tumor location with respect to the parasympathetic/sympathetic origin of the tumor, and correlation with the biochemical profile and the appropriate terminologies are discussed in detail in parts A and B. Therefore, the anatomic location of the tumor must be clearly specified in the synoptic report with the appropriate classification based on location.
Similar to other guidelines, tumor size is a required field in surgical pathology reports. Numerous reports have indicated that malignant tumors are heavier and larger than tumors with benign behavior[5,40,98-102]. Although the tumor size and weight are not universally considered independent parameters, a cut-off of 5-6 cm diameter and 80-150 gram weight have been suggested to predict malignant behavior [99-102].
The issue of multifocality is of interest and should be included in the synoptic report. Patients with multiple PGLs should be investigated for the possibility of underlying genetic susceptibility and thus genetic testing for *RET*, *NF-1*, *VHL*, *SHDx*, *TMEM127*, *MAX*, and *KIF1Bβ* mutations should be considered[22,23,36,37,103,104]. While the value of systematic genetic screening for "sporadic" cases remains controversial, clinical features including family history, along with the biochemical and morphological features

(multifocality, adrenal medullary hyperplasia, thick capsule, clear cell morphology), and immunoprofile (loss of *SDHB* and *SDHA* expression)[104,105] (see parts B, E, H and J) can provide important insight to determine which gene(s) should be screened preferentially in patients with PCCs and/or extra-adrenal PGLs. Multifocality includes multiple PCCs in the same adrenal.

C: Histologic Features

Regardless of sympathetic or parasympathetic origin, PGLs usually exhibit overlapping morphologic features. They display a variety of growth patterns and cytological features[2-6]. While sympathetic paragangliomas and pheochromocytomas consist of polygonal cells, so-called "chromaffin" cells that exhibit amphophilic to basophilic cytoplasm, parasympathetic tumors consist of polygonal cells, so-called "chief cells" that often have relatively clearer cytoplasm than their sympathetic counterparts. However, overlapping of these cells is often seen in these tumors. Similar to other endocrine lesions, oncocytic change, spindle cell morphology and lipid cell degeneration leading a clear cell morphology that mimics cortical lesions can also be seen in these neoplasms[3,5,106].

Genotype-phenotype correlations highlighted that VHL-related tumors contain usually a thick vascular capsule, hyalinized and myxoid stroma, round tumor cells intermingled with small vessels, cells with predominantly amphophilic and clear cell cytoplasm, absence of intracytoplasmic hyaline globules, lipid degeneration[106] and lack of nuclear atypia or mitoses[3,5].
The term "composite" should be used when a tumor combines features of PGL or PCC with those of malignant peripheral nerve sheath tumor, ganglioneuroma, ganglioneuroblastoma and neuroblastoma. Comprehensive data related to neuroblastic and related component should be reported by using the designated synoptic checklist[96].
In this setting, corticomedullary tumors, cauda equina PGLs showing ependymal differentiation as well as gangliocytic PGLs that include Schwann-like cells and ganglion cells do not qualify as composite tumors[3,4]. Moreover, scattered mature ganglion cells seen in PCCs/PGLs should not be misinterpreted as a component of a composite tumor[3-6].

No single histological parameter is able to predict malignant behaviour in PGLs and PCCs[2-6]. Tumor necrosis is uncommon in these tumors and degenerative changes should not be taken as necrosis. However, expanded large confluent nests with central comedo necrosis, which are at least three times greater than conventional small nests, have been described in some malignant PCCs/PGLs[3-6]. Therefore, a distinction should be made between focal (small microscopic foci or single cell necrosis) and extensive (central, expansive or "comedo" necrosis).
Increased mitoses (>3/10 HPF) and atypical mitotic figures have been reported in some malignant cases[3-5], but mitoses are usually very rare even in malignant cases. There is currently no standard approach to mitotic count in PCC/PGL. On the basis of established methodology for other neuroendocrine tumors, it is recommended that mitotic count should be based upon counting 50 HPF (40x objective) and in the area of highest mitotic activity, and reported as number of mitoses per 10 HPF.

F: Encapsulation and Invasiveness

According to the 2004 World Health Organization (WHO) classification of endocrine neoplasms, malignancy of PCCs and extra-adrenal PGLs is defined by the presence of metastases to sites where paraganglial tissue is not normally found[3]. Although local gross invasion into the adjacent organs is considered in the definition of malignancy proposed by the 2007 Armed Forces Institute of Pathology (AFIP) fascicle[4], this is not regarded as a strong predictor of metastases and therefore it is not integrated in the 2004 WHO classification[3,5,6]. Moreover, unlike other neoplasms, vascular invasion is also not universally accepted as an unequivocal predictor of malignant potential in PGLs and PCCs[3,5,6]. However, it is important to document the invasiveness of these tumors. Strict criteria to diagnose vascular invasion (intravascular tumor cells associated with thrombus) and capsular invasion (transcapsular) should be applied as they are in other endocrine organs[107]. As discussed in part E, the presence of a thick vascular capsule may raise the suspicion of a VHL-related PGL[3,5,6].

G: Metastases

An extra-adrenal location, large size, and the presence of *SDHB* mutations are all important risk factors for metastatic spread[34,38,40,63,98]. High rates of malignancy in tumors associated with *SDHB* mutations can be fully accounted by both their typically extra-adrenal location and large size [40]. While tumors arising from head and neck paragangliomas are much less often metastatic, mediastinal and intraabdominal PGLs appear to often be associated with metastatic disease[3,5,55,98].

The diagnosis of metastasis is appropriate when dealing with a site where no paraganglial tissue is observed; it is crucial to remember the normal anatomic distribution of paraganglia as discussed in part A, to consider the possibility of multifocal primaries. The pathology report should state the total number of lymph nodes examined, the number of nodes with metastases, and nodal involvement should be reported as macrometastasis, micrometastasis or isolated tumor cells based on the size of the metastatic deposit. While the determination of the nodal disease is easy, the assessment of distant metastasis can be challenging in the setting of multifocal disease, since primary PGLs do also occur in rare anatomical sites such as thyroid, pituitary, gallbladder, and lung[4,6,108-110]. Therefore, these rare locations should not be considered metastatic ab initio.

H: Role of immunohistochemistry

Positivity for tyrosine hydroxylase, which is the rate limiting enzyme in the synthesis of catecholamines, is very helpful to distinguish PGLs from other neuroendocrine carcinomas, which can also be negative for cytokeratins[6]. However, positivity for chromogranin-A and tyrosine hydroxylase is usually weaker and more variable in parasympathetic PGLs than in sympathetic PGLs and is sometimes negative[6]. Some of these tumors selectively express chromogranin B.

S100 protein is typically used to highlight the sustentacular network in PGLs; however, the reactivity pattern is usually variable. It is of note that epithelioid endocrine cells and spindled Schwann-like cells of gangliocytic PGLs can be positive for cytokeratin and S100 protein, respectively[3,4]. Moreover, cauda equina paragangliomas, which are usually intradural lesions limited to the filum terminale, may show ependymal and neuronal differentiation and can be positive for cytokeratin[3,4,111].

There is currently no standard approach to scoring Ki-67 in PCC and PGL. On the basis of established methodology for other neuroendocrine tumors, it is recommended that Ki-67 index should be reported as percentage of positive tumor cells in area of highest nuclear labeling.

Loss of *SDHB* expression is regarded as a surrogate marker for some of the familial PGL syndromes caused by *SDHx* mutations[105], therefore immunohistochemical testing for *SDHB* has become a part of the routine assessment of these lesions in many centers. Moreover, the use of *SDHB* antibody not only allows the identification of *SDHx* related tumors, but also provides prognostic data, due to the high rate of malignancy associated with *SDHB*-driven PGLs [34,38,63,91]. Recently, it was also demonstrated that *SDHA* immunohistochemistry is also very useful to reveal the presence of *SDHA* germline mutations[112]; PGLs associated with germline *SDHA* mutation show negative staining for *SDHA* as well as *SDHB*.

6. MANAGEMENT ALGORITHMS

6.1 Indications for biochemical screening for Pheochromocytomas/Paragangliomas (PPGLs)

The following are the indications for biochemical screening for PPGLs:

1. Typical signs and symptoms of catecholamine excess.
2. As part of the diagnostic workup of individuals suspected of having secondary hypertension of an endocrine cause.
3. Familial syndrome or germline mutation associated with PPGLs.
4. Adrenal incidentaloma.
5. Follow up of patients with previously diagnosed PPGLs

It is important that all patients with incidentally discovered adrenal lesions undergo appropriate functional testing before considering a biopsy. Needle biopsies of adrenal lesions are rarely helpful in establishing a diagnosis[113] and may result in serious complications as well as increase operative difficultly due to an inflammatory reaction at the biopsy site of these highly vascular tumours [114].

6.2 Clinical Diagnosis

The clinical diagnostic approach to PPGLs is to include the following aspects:

1. Full history and clinical examination.
   a. Presence of acute and/or chronic symptoms that may suggest catecholamine excess including hypertension, previous arrhythmias, dilated cardiomyopathy, myocardial infarctions, and Takotsubo pattern cardiomyopathy[115,116]. The presence of diabetes that may be secondary to catecholamine excess must also be assessed.
   b. Presence of conditions that may lead to false positive biochemical testing such as severe congestive heart failure and sleep apnea.
   c. Full list of medications.
   d. Presence of family history of PPGLs, MEN2, VHL, and NF-1.
   e. A physical exam looking for specific phenotypic features suggestive of a hereditary syndrome: thyroid masses, neck masses, marphanoid habitus, mucus neuromas, *cafe-au-lait* macules, neurofibromas, and freckling in the axillary of inguinal regions.

2. Assessment of functionality by means of urine catecholamines and metanephrines.
   a. Urine catecholamines and metanephrines are measured with high liquid chromatography. Direct interference of medications is uncommon and so there is no absolute indication to stop any of them (reviewed in biochemical diagnosis section). If a result is positive and a medication effect is suspected testing can be repeated once the patient has stopped the drug.
   b. Urine should be collected in the appropriate containers. Collection should start in the morning. The first morning urine ought be discarded and the

time of collection initiates the moment the first sample is collected and finishes 24 hours after.

c. Levels of urine fractionated metanephrines or urine fractionated catecholamines >2 times the upper limit of normal are always assumed to represent true positive results unless proven otherwise. Borderline positive results may be a reflection of low tumor burden or a false positive. These patients merit appropriate follow up to clarify the aetiology of the biochemical abnormality. In some instances that is not possible, but lack of progression over time as well as negative functional and anatomic imaging are indicative of a false positive result.

Is important to mention that when a genetic syndrome is suspected appropriate assessment of all of its components is warranted. The management of medullary thyroid carcinoma has been previously established in our institutional guidelines. Management of other endocrine and non-endocrine associated complications is beyond the scope of these guidelines.

6.3 Localization

Anatomic and Functional

Once the biochemical diagnosis has been established the next step is to proceed with localizing studies. The only exception to this occurs when there is suspected non-functional disease, as it is the case of head and neck paragangliomas. Previous knowledge of germline disease helps in deciding the extent of initial imaging. Computed tomography (CT) with contrast is routinely used as the first imaging modality to localize PPGLs. Allergy to contrast agents or pregnancy are indications to consider magnetic resonance imaging (MRI) instead.

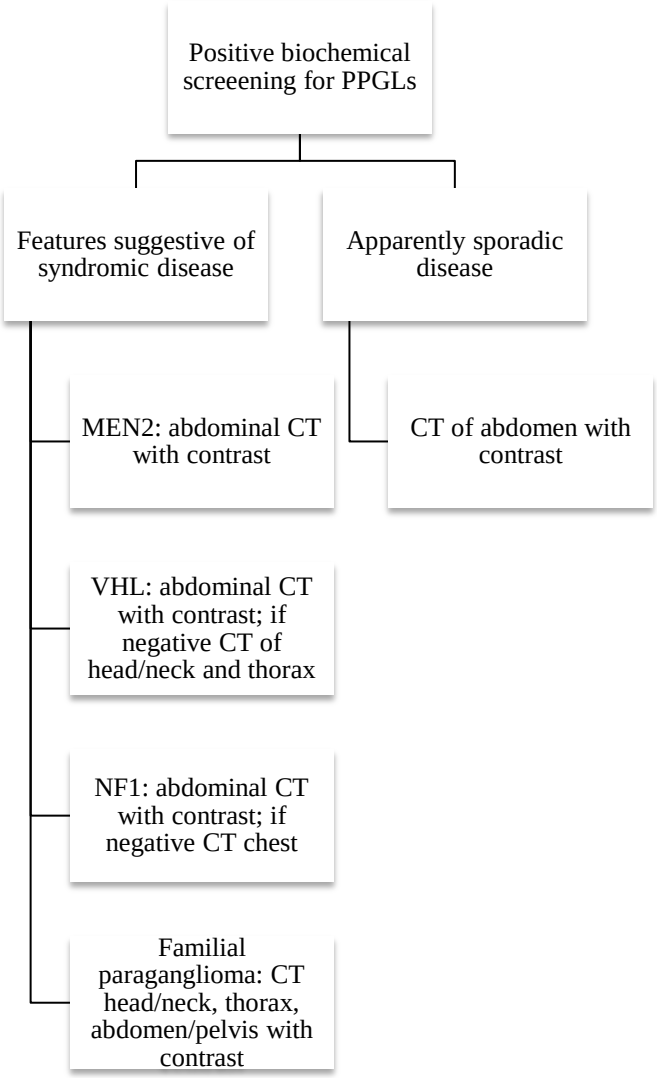
Suspected metastatic disease

Once the tumor has been localized further imaging may be warranted in case there is suspicion of metastatic disease. Characteristics of sympathetic paragangliomas that should alert to the possibility of metastases include:

a. Localization in the infradiaphragmatic paraaortic region, organ of Zuckerkandl, mediastinum, and bladder[55].
b. Larger primary tumor size[64,117]. Tumors < 5 cm in size are less likely to be metastatic[55].

Localization of metastatic disease is currently initially done with CT, MRI and occasionally ^{131}I-MIBG scintigraphy. Nevertheless, there is strong evidence to support ^{18}F-FDG PET as the modality of choice in this context[64,92] and we are presently working to make it readily available.

Figure 1. Initial imaging choice according to phenotypic features or known genotype



Preparation for ^{131}I-Meta-iodobenzylguanidine (^{131}I-MIBG) Scintigraphy

^{131}I-MIBG scintigraphy is available at our institution as a first line functional imaging modality in patients at increased risk for metastatic PPGLs, and/or those individuals at high risk of multifocal and/or extra-adrenal disease. With the advent of peptide receptor radionuclide therapy the role of ^{131}I-MIBG will extend to the selection of patients that are suitable for MIBG therapy.

The following precautions should be taken for appropriate patient preparation:

1. Pregnancy is a contraindication for the test. Breastfeeding should be stopped indefinitely once 131 I-MIBG has been injected[118].
2. Thyroid blockade should be started 1 day prior to the injection of 131 I-MIBG and continued for five days thereafter. Potassium iodine 65 mg tablets are used for that purpose and the dose is 130 mg daily[118].

3. MIBG structurally resembles guanethidine (an adrenergic neuron blocker) and noradrenaline and for that reason is taken up by the adrenal medulla and sympathetic neurons[119]. There are several that interfere with the uptake of MIBG. They should ideally be stopped before the study is done in order to obtain more reliable results but the risk/benefit of such approached should always be weighed[120].

Table 2. Proposed time of discontinuation of drugs interfering with ^{131}I-MIBG uptake	
Drug	Weeks of suspension prior to scintigraphy
Labetalol	3
Nifedipine, amlodipine	2
Diltiazem, verapamil	2
Reserpine	2
Clomipramine, desipramine, dosulepine, imipramine, maprotiline	1 to 3
Citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline	1 to 3
Haloperidol, droperidol, levomepromazine, chlorpromazine, promethazine, fluphenazine	3 to 4
Tramadol	1 to 2
Trazodone	3 to 4
Chlorphenamine, phenylpropanolamine, pseudoephedrine	1 to 2
Ethylephrine	1 to 2
Adapted from *Eur Rev Med Pharmacol Sci 2013;17:1326-33* [120]	

Preparation for 18F-FDG PET

As mentioned previously the goal for the near future is that ^{18}F-FDG PET will substitute ^{131}I-MIBG scintigraphy as the functional imaging of choice for PPGLs. The following precautions should be taken for appropriate patient preparation:

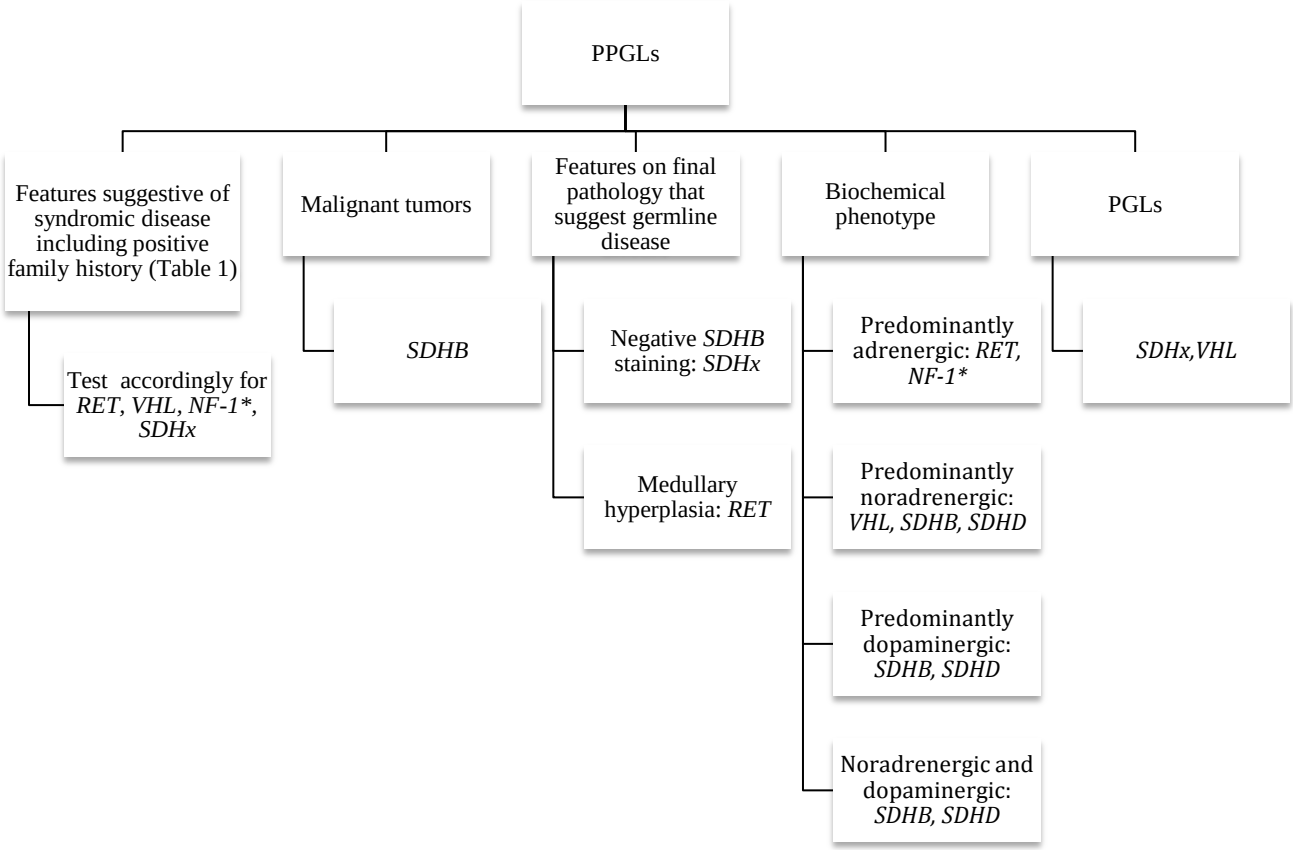
1. In general it is not advised that pregnant women undergo this study. Breast-feeding should be discontinued for 12 hours after imaging[118].
2. Glucose levels in patients with diabetes should be normalized.
3. All patients must fast for at least 6 hours before the intravenous administration of ^{18}F-FDG[118].

6.4 Genetic testing

As discussed in the genetics section, genetic testing should be done in an ordered manner and based on the information that is available (biochemical phenotype, syndrome features, surgical pathology)[32,41,57,66]. Given the high frequency of germline mutations all patients should be aware of the possibility of familial disease and offered genetic testing. Nevertheless, in individuals > 50 years with unilateral pheochromocytomas the possibility of finding a mutation is very low[32].

The most frequent mutations have been included in the following algorithm but further testing may be considered when indicated. Of note, neurofibromatosis type 1 is not included in because the diagnosis is usually made based on clinical parameters.

Figure 2. Algorithm for genetic testing



* NF-1 genetic testing is not routinely done and the diagnosis of the syndrome is based on pre-established criteria[1]

6.5 Drugs that Should Be Avoided in Patients with PPGLs

The following drugs should generally be avoided in patients with PPGLs as they might exacerbate symptoms:[121,122]

1. Beta blockers in the absence of previous appropriate alpha blockade.
2. Dopamine 2 receptor antagonists such as metochlopramide.
3. Tricyclic antidepressants.
4. Monoamine oxidase inhibitors.
5. Sympathomimetics.
6. Peptide and corticosteroid hormones.

6.6 Preoperative Preparation and Postoperative Considerations

Patients with pheochromocytomas and sympathetic paragangliomas have a higher cardiovascular risk compared to patients with essential hypertension[123]. Cardiovascular complications occur in about 19% of patients; atrial fibrillation, myocardial ischemia and heart failure are the most common events[115]. Therefore, a complete cardiovascular evaluation should be done in every patient and in most instances an echocardiogram should be obtained[124,125].
Data from the 1970s clearly showed that alpha blockade changed the outcome of surgery by markedly reducing mortality rates in hypertensive patients[126]. However, more recent studies seem to suggest that alpha blockade is not that advantageous probably due to advances in anaesthetic management including the availability of faster acting vasoactive drugs[127,128]. Furthermore, there is evidence from a small randomized trial that normotensive patients may not be benefited from preoperative alpha blockade[129]. This information needs to be analyzed with caution, as we know that tumor manipulation during surgery is associated with release of catecholamines into the bloodstream resulting in severe hypertension and arrhythmias[130]. Preoperative medical treatment should be tailored to every single patient and consideration of underlying conditions such as severe heart disease should be taken into consideration. Patients with functional PPGLs that are going to undergo surgery should be prepared one to two weeks before the procedure[131]. The goal of preoperative treatment is to normalize blood pressure and heart rate as well as to expand intravascular volume (the latter can also be easily accomplished by loading the patient with saline before the surgery). Usually a week is enough time achieve these goals and there is evidence that prolonged preparation (>14 days) is not more effective in preventing severe intraoperative hypertensive episodes[130].

The following are the steps that are taken before surgery:

1. Full cardiologic examination. All patients must have an electrocardiogram and an echocardiogram will usually also be requested.
2. Monitoring of blood pressure and heart rate. All patients should be instructed to take their blood pressure twice a day. This should be done while the patient is supine and 3 minutes after standing up.
3. Repletion of intravascular volume. Alpha-adrenergic blockers take 2 to 3 weeks to expand intravascular volume[132] and so a high sodium diet and appropriate hydration should be part of treatment.

4. Alpha blockade. This should be started one to two weeks before surgery. The agent that has been typically used in many institutions has been phenoxybenzamine. Nevertheless, access to it is sometimes difficult and other alpha-blockers are readily available. Additionally, selective alpha-1 blockers such as doxazosin have some advantages. For example, doxazosin is not typically associated with reflex tachycardia (except if the tumor is predominately adrenergic) and it has a shorter half-life than phenoxybenzamine allowing for more flexibility[133]. Doxazosin is normally started at a dose of 1 to 2 mg and titrated up to achieve an orthostatic BP <140/90 mmHg but >90/60 mmHg.
   Is important to note that in patients with an exclusively dopaminergic phenotype alpha blockade may not be the most appropriate approach[43,134] although there is not enough data to support that statement. However, especially in normotensive patients calcium channel blockade should be considered instead.
5. Beta blockade. Once appropriate alpha blockade has been accomplished, beta blockade is initiated if patients have tachycardia and/or as adjunctive therapy in the management of hypertension.
6. Calcium channel blockade. These agents do not produce hypotension and are able to prevent catecholamine induced coronary vasospasm[83]. They may be used in normotensive patients or in addition to alpha and beta blockade in order to control hypertension.

Postoperative considerations

After surgery ongoing monitoring of blood pressure and heart rate is fundamental. Antihypertensive drugs must be adjusted accordingly. Additionally, glycemia should be monitored and antidiabetic treatment may need to be adjusted as the diabetogenic effects of catecholamines tapers off.

For patients who have had a bilateral adrenalectomy appropriate glucocorticoid and mineralocorticoid replacement therapy must be started. Titration of the doses will be based predominantly on clinical findings and when indicated aided with biochemical testing, i.e. renin levels and 24 h urine free cortisol.

6.7 Surgical management

Minimally Invasive Surgery

Minimally invasive surgery is the preferred approach for removal of localized pheochromocytomas in almost all cases, and for many paragangliomas. The advantages of minimally invasive surgery include less postoperative pain, shorter hospital stay, and faster return to full activities, as compared with open surgical approaches[135]. Open surgery is reserved for very large tumors, tumors with invasion of adjacent structures, or tumors in locations not easily accessible through minimally invasive approaches.

There are two commonly used minimally invasive approaches for adrenalectomy; a conventional laparoscopic (transperitoneal) approach, and a retroperitoneoscopic (retroperitoneal) approach. While surgeons in North America have traditionally been

more comfortable with transperitoneal laparoscopy, the technique of retroperitoneoscopic adrenalectomy, as described by Martin Walz,[136] has become increasingly popular in expert centres.

In conventional laparoscopic surgery, the patient is usually positioned on the side, and the peritoneal cavity is insufflated with carbon dioxide gas to create a working space. Overlying organs are mobilized, and the adrenal gland is identified. Early ligation of the draining vein is a preferred strategy in pheochromocytoma surgery; in practice, it is usually not possible to ligate the adrenal vein prior to exposure of the adrenal gland and division of much of the arterial supply. In retroperitoneoscopic surgery, the patient is placed in the prone jackknife position. A working space in the retroperitoneum is developed below the eleventh and twelfth ribs, and high-pressure carbon dioxide insufflation of the perirenal fat within Gerota's fascia is done to create a working space. The superior pole of the kidney is widely mobilized, exposing the adrenal gland, which is then devascularized and removed. The venous drainage of the adrenal is highly predictable, with a single draining vein in nearly all cases, arising infero-medially in the left adrenal from the left renal vein and supero-medially in the right adrenal gland from the inferior vena cava.

The majority of abdominal paragangliomas are located along the aorta from just above the renal hilum to the aortic bifurcation[137]. Paragangliomas may be more difficult to resect than pheochromocytomas, because of their eccentric location, unpredictable blood supply, and extensive surrounding arterial network. While paragangliomas may be approached by retroperitoneoscopic or laparoscopic surgery, only those paragangliomas located well above the renal hilum are amenable to retroperitoneoscopic surgery; the remainder are best approached by laparoscopy, or by open surgery (see Figure 3).

Cortical-sparing or partial adrenalectomy has been reported in bilateral pheochromocytomas. Subtotal adrenalectomy for pheochromocytoma/paragangliomas is controversial, because of the risk of recurrent disease in the medullary remnant with germline disease, and uncertainty about the risk of adrenocortical insufficiency. In one series of 66 patients (most with genetic mutations), 91% did not require adrenal replacement postoperatively; the remaining six required corticosteroid supplementation. After a median follow up of 48 months, one patient with persistent disease required reoperation and none developed recurrence[138]. Recurrence after partial adrenalectomy is easily addressed through retroperitoneoscopic surgery, which is an advantage of this approach over laparoscopic adrenalectomy for recurrent pheochromocytoma.

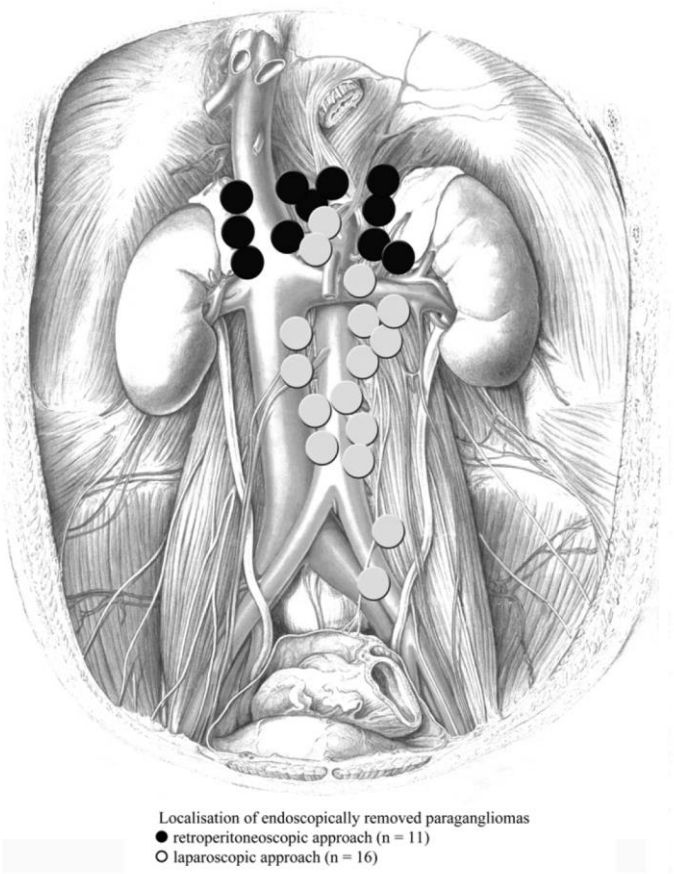


Figure. Location of paragangliomas removed by retroperitoneoscopic and laparoscopic approach[139]. Tumors above the renal hilum are accessible by a retroperitoneoscopic approach. Tumors below the renal hilum are best approached through laparoscopic surgery.

6.8 Medical Treatment for Malignant Pheochromocytomas/Paragangliomas

The optimal treatment of PPGLs is surgical. Nevertheless, in the context of malignant disease in many instances surgery is not curative and/or not possible and for that reason palliative medical/radiation therapy needs to be considered. The appropriate moment to start such therapy has not been well established. Furthermore, both recent and older data suggests that while some tumors progress very rapidly there is a subset that tends to progress slowly[140] and a watch and wait approach may be more appropriate[64]. ^{131}I-MIBG, chemotherapy, and targeted therapy constitute some of the mainly used medical treatments for malignant PPGLs[141,142]; their usage depends on local experience and availability. At present time at our institution patients with malignant PPGLs are considered for medical treatment with chemotherapy or targeted therapy in the form of sunitinib (Sutent®).

Sunitinib is a multi-tyrosine kinase inhibitor with direct antitumor and antiangiogenic activities mainly due to targeting of the following tyrosine kinase receptors: vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF), v-kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homolog (KIT), fms-related tyrosine kinase 3 (FLT3)[143] and rearranged during transfection (RET)[144]. This drug was initially accepted by the United States Food and Drug Administration (FDA) in 2006 and is currently approved for the treatment of gastrointestinal stromal tumors, advanced renal cell carcinoma, and progressive well-differentiated pancreatic neuroendocrine tumors[145]. Even though targeted therapy is generally associated with less toxicity when compared to traditional chemotherapy, sunitinib's multikinase inhibition may result in several adverse effects (Table 3). Most adverse effects are not severe but for significant reactions discontinuation (permanent or temporary) of therapy or dose reductions should be considered. It should also be noted that sunitinib is metabolized in the liver by CYP3A4 and CYP3A5[146] and for that reason concomitant use of strong CYP3A4 inhibitors such as ketoconazole should be avoided.

Table 3. Selected Adverse effects and Special Considerations When Using Sunitinib

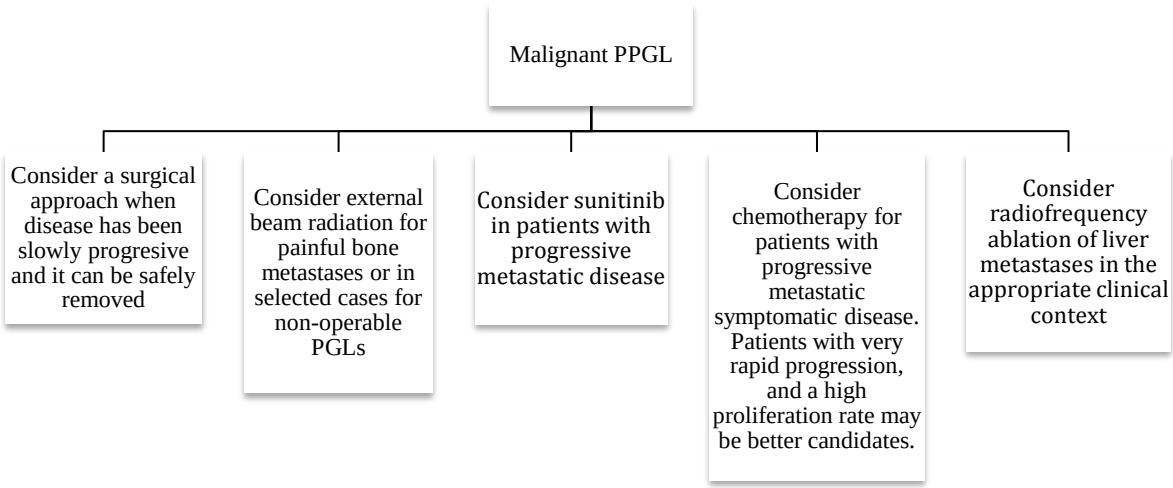
Adverse effects	Recommendations
• Inhibition of angiogenesis in non-tumorous tissues	• Temporarily stop sunitinib in patients undergoing major surgical procedures[145]. • Avoid use in pregnant women.
• Fatigue	• Fatigue is usually mild and rest will alleviate it.
• Diarrhea	• Loperamide 2 mg[147] before the scheduled dose of sunitinib. • If loperamide does not result in improvement of symptoms diphenoxy-late hydrochloride/atropine sulfate (5 mg) may be used[147].
• Hand foot syndrome	• Avoid extreme changes in temperature, tight shoes, diphenhydramine-containing creams, topical anesthetics[148].

	• Use lanolin-based creams or urea-based lotions[147].
• Hypertension [149]	• Optimize blood pressure control before initiation of treatment[150]. • Monitor blood pressure during treatment and treat persistent hypertension[147,150].
• Hypothyroidism[151]	• Periodic assessment of TSH. Thyroid hormone supplementation therapy should be initiated when indicated. Hypothyroidism may resolve after discontinuation of sunitinib[152].
• Hepatotoxicity	• Periodic assessment of liver enzymes and bilirrubin.
• Renal toxicity[149]	• Periodic assessment of creatinine and urinalysis.
• Adverse cardiac events including congestive heart failure and arrhythmias	• Monitor for symptoms and signs of congestive heart failure. • Obtain a baseline electrocardiogram and be particularly careful with patients that have a prolonged QT. • Correct electrolyte abnormalities.
• Anemia, leucopenia and thrombocytopenia[153]	• Periodic assessment of complete blood cell count.

Sunitinib has not yet been approved by the FDA for the treatment of metastatic PPGLs. However, several experienced centres including our own have been using it with an acceptable degree of success[117,154-157]. Moreover, PMH/University Health Network, is the lead site of an ongoing phase II open label study of sunitinib[158]. In the largest published study to date, 17 patients received treatment with sunitinib for metastatic PPGLs and 47% of showed some benefit (disease stabilization or tumor size reduction)[155]. Some patients also had improvement of their hypertension. The benefit is mostly seen in patients with *SDHB* mutations as opposed to patients with sporadic disease[155]. Improvement of hypertension is probably related to inhibition of catecholamine synthesis[159].

In regards to chemotherapy, dacarbazine-based and cyclophosphamide-based regimens combined with vincristine or doxorubicin have been more widely studied[160,161]. There are also scattered case reports and series suggesting that PPGLs respond to a variety of alternative agents such as temozolamide alone[162], single agent gemtabicine[163], doxurobicin plus streptozocin[164], or paclitaxel alone[165]. In general, just as it is observed with targeted therapy, anatomic and clinical/biochemical response to treatment is around 50%[140,160,161]. Since chemotherapy regimens may improve clinical and biochemical outcomes, it should be considered in patients that remain symptomatic after optimized treatment of their pain and symptoms of catecholamine excess [140].

Figure 3. Approach to the Patient with Malignant Pheochromocytoma/Paraganglioma (PPGL)



7. RADIATION THERAPY

External beam radiation therapy May be useful in palliating symptoms from metastatic or locally recurrent pheochromocytoma especially painful bone metastases.

External beam radiation however has an important role in the management of paragangliomas of the head and neck region, especially glomus tumours in the jugular foramen. A dose of 45Gy in 25 fractions may achieve a response rate of more than 90%, however response is slow. Such tumours are usually treated by the head and neck group of the department of radiation oncology.

8. ONCOLOGY NURSING PRACTICE AND SUPPORTIVE CARE

8.1 Nursing Patient Care

Refer to general oncology nursing practices

8.2 Patient Education

The Carcinoid Neuroendocrine Tumour Society of Canada (CNETS Canada) is working towards creating an environment in which people who are dealing with neuroendocrine tumors (including pheochromocytomas and paragangliomas), especially the newly diagnosed, are met with support and information. CNETS Canada draws on the medical community to provide support for all individuals dealing with the disease.

CNETS goals and objectives include facilitating communication among neuroendocrine tumor patients, providing credible information about the disease, providing emotional support, and assisting patients with voicing their needs to health care professionals and those who are responsible for health care policy. For more information please check: http://www.cnetscanada.org/index.html.

CNETS Canada liaises with groups with similar or corresponding mandates including The Pheo/Paraganglioma group. For more information, please check: http://www.pheoparatroopers.org

8.3 Psychosocial Care

Refer to general oncology psychosocial care

9. FOLLOW UP CARE

Sporadic and familial forms of PPGLs may be recur and/or be malignant. Familial forms may also be associated with multiple tumors that can be metachronic or synchronic. These factors obligate lifetime monitoring. All patients are followed with once a year urine metanephrines and catecholamines. Testing may be done sooner than that if the individual becomes symptomatic.

Imaging is recommended whenever there is biochemical evidence of disease. It is also indicated if there is suspicion of clinically silent disease. For patient with germline mutations in *SDHC* and *SDHFA2*, in which tumors are usually non-functional, the probability of malignant disease is close to cero and so frequent imaging is not necessary. In patients harbouring *SDHB* mutations once a year imaging will be done. MR will be used in patients that require frequent imaging to avoid excessive radiation exposure.

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