

Mini-Review

Metastatic Pheochromocytomas and Abdominal Paragangliomas

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Abbreviations: ACTH, adrenocorticotropic hormone; CR, complete response; CT, computed tomography; FDG, fluorodeoxyglucose; ¹⁸F-FDG, ¹⁸F-fluorodeoxyglucose; ¹⁸FDOPA, ¹⁸F-flourodihydroxyphenylalanine; GAPP, Grading System for Adrenal Pheochromocytoma and Paraganglioma; HED, ¹¹C-hydroxy-ephedrine; HU, Hounsfield units; MEN2, multiple endocrine neoplasia type 2; MIBG, meta-iodobenzylguanidine; MRI, magnetic resonance imaging; PASS, Pheochromocytoma of the Adrenal Gland Scaled Score; PD1, programmed death-1; PD-L1, programmed death-ligand 1; PET, positron emission tomography; PFS, progression-free survival; PPGLs, pheochromocytomas and paragangliomas; PR, partial response; PRRT, peptide receptor radionuclide therapy; RECIST, response evaluation criteria in solid tumors.

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Abstract

Context: Pheochromocytomas and paragangliomas (PPGLs) are believed to harbor malignant potential; about 10% to 15% of pheochromocytomas and up to 50% of abdominal paragangliomas will exhibit metastatic behavior.

Evidence Acquisition: Extensive searches in the PubMed database with various combinations of the key words *pheochromocytoma*, *paraganglioma*, *metastatic*, *malignant*, *diagnosis*, *pathology*, *genetic*, and *treatment* were the basis for the present review.

Data Synthesis: To pinpoint metastatic potential in PPGLs is difficult, but nevertheless crucial for the individual patient to receive tailor-made follow-up and adjuvant treatment following primary surgery. A combination of histological workup and molecular predictive markers can possibly aid the clinicians in this aspect. Most patients with PPGLs have localized disease and may be cured by surgery. Plasma metanephrines are the main biochemical tests. Genetic testing is important, both for counseling and prognostic estimation. Apart from computed tomography and magnetic resonance imaging, molecular imaging using ⁶⁸Ga-DOTATOC/DOTATATE should be performed. ¹²³I-MIBG scintigraphy may be performed to determine whether ¹³¹I-MIBG therapy is a possible option. As first-line treatment in patients with metastatic disease, ¹⁷⁷Lu-DOTATATE or ¹³¹I-MIBG is recommended, depending on which shows best expression. In patients

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with very low proliferative activity, watch-and-wait or primary treatment with longacting somatostatin analogues may be considered. As second-line treatment, or first-line in patients with high proliferative rate, chemotherapy with temozolomide or cyclophosphamide + vincristine + dacarbazine is the therapy of choice. Other therapies, including sunitinib, cabozantinib, everolimus, and PD-1/PDL-1 inhibitors, have shown modest effect.

Conclusions: Metastatic PPGLs need individualized management and should always be discussed in specialized and interdisciplinary tumor boards. Further studies and newer treatment modalities are urgently needed.

Key Words: malignant, histology, imaging, treatment, diagnosis, genetics

Pheochromocytomas and paragangliomas (PPGLs) are rare tumors, which may produce catecholamines, epinephrine, norepinephrine, and dopamine. Pheochromocytomas occur in the adrenal medulla, arising from chromaffin cells, while paragangliomas arise from chromaffin cells in sympathetic or parasympathetic ganglia in the chest, abdomen, or pelvis or from parasympathetic ganglia in the heads and neck (1, 2). Although all PPGLs are believed to harbor malignant potential, about 10% to 15% of pheochromocytomas and up to 50% of abdominal paragangliomas will become metastatic (3). This review will focus on the diagnostic and therapeutic attributes of metastatic pheochromocytomas and catecholamine producing (abdominal) paragangliomas.

Epidemiology and Incidence

The yearly incidence of pheochromocytomas is around 2 to 8 per million with a general prevalence of 1:2500 to 1:6500 (4, 5), but they are more common in certain groups of patients. PPGLs are found in 0.2% to 0.6% of patients with sustained hypertension (6, 7), but sustained hypertension is only present in about one-half to two-thirds of all patients with these tumors (8, 9). In patients with adrenal incidentalomas, 0.6% to 4.2% have a pheochromocytoma (10-12). In familial syndromes, the prevalence of PPGLs can be much higher; for instance, in multiple endocrine neoplasia type 2 (MEN2), around 50% of patients with Takotsubo syndrome (an acute cardiac entity resembling clinically that of an acute coronary syndrome) of unclear cause, PPGLs may be prevalent (14).

Clinical Presentation

The majority of PPGLs are currently diagnosed through the workup of an incidentaloma, secondly due to symptoms of catecholamine excess, and lastly during catecholamine screening in a patient with an established familial syndrome (eg, MEN2, von Hippel Lindau syndrome, neurofibromatosis type 1, and patients with hereditary PPGL due to susceptibility gene mutations in succinate dehydrogenase [*SDHB*, *C*, *D*], *TMEM-127*, *MAX*, *FH*, *EPAS1/HIF-2a*, or *MDH2*) (2, 8, 15-17). Rarely, PPGLs may also produce other hormones, most commonly adrenocorticotropic hormone (ACTH) and may then present with clinical findings consistent with, eg, Cushing syndrome (18-20).

Thus, the increasing use of imaging has propelled the detection of patients with PPGLs through the finding of an incidentaloma on computed tomography (CT) or magnetic resonance imaging (MRI) scan performed as part of investigation for other conditions. In recent series, 61% to 64% presented primarily as incidentalomas (8, 16). PPGLs may secrete epinephrine and norepinephrine, which often results in diffuse and nonspecific symptoms that can be a challenge for clinicians (2, 8). Only 27% to 32% of patients with PPGLs are discovered due to symptoms of catecholamine excess, mostly since these have not been recognized (8, 16), with only 12% being asymptomatic (8). Symptoms include headache, hypertension, pallor, palpitations, sweating, diaphoresis, and anxiety. Paroxysmal symptoms occur in around two-thirds of the patients (8). The classic triad with attacks of headache, palpitation, and sweating is found in only 17% to 24% of patients (8, 21). Other symptoms include chest pain, psychiatric symptoms, hyperglycemia, constipation, and syncope. Uncommon presenting symptoms include Takotsubo syndrome (22-24), other life-threating cardiovascular events (25), and preeclampsia (26).

Diagnosis

Biochemical Diagnosis

Elevated levels of epinephrine are seen only in pheochromocytomas, while norepinephrine may be elevated both in pheochromocytomas and paragangliomas (17). Epinephrine and norepinephrine as well as their metabolites, metanephrine and normetanephrine, can be measured in 24-hour urine collection samples. The best biochemical method for diagnosing PPGLs is, however, free plasma metanephrine and normetanephrine, with a sensitivity of 92% to 100% and a specificity of 80% to 100% (27, 28). Chromogranin A, which is produced by many neuroendocrine tumors, is also secreted by PPGLs and in the absence of renal insufficiency has a sensitivity of 98% and a specificity of 97%. The best combination of sensitivity and specificity is obtained by combining plasma chromogranin A and metanephrines (29). Another catecholamine metabolite, methoxytyramine, measured in plasma, has been shown to be an important biomarker for metastatic PPGLs (30).

Imaging

A CT scan (Fig. 1) is often the first modality on which an adrenal mass is detected. Pheochromocytomas may be solid or cystic to various degrees (31). Spherical shape, sharp necrosis, and "ring sign" are indications that the tumor is a pheochromocytoma (32). Pheochromocytomas can be ruled out with 99% certainty if an adrenal tumor on unenhanced CT imaging has a value ≤ 10 Hounsfield units (HU) (33-36). After iodine contrast has been given, pheochromocytomas usually show strong enhancement, more than 130 HU (35). On MRI, the signal intensity in T1- and T2-weighted images may vary considerably. Cystic and hemorrhagic pheochromocytomas are hyperintense on T2-weighted images, yet this classical pattern is relatively uncommon (35). A recent report indicates that MRI with diffusion-weighted imaging has high sensitivity in identifying PPGLs, and can even detect small tumors, down to 5 mm (37).

Functional imaging may be performed with ¹²³I-metaiodobenzylguanidine (¹²³I-MIBG) (Fig. 2) scintigraphy, ⁶⁸Ga-DOTATOC (Fig. 3) or ⁶⁸Ga-DOTATATE positron emission tomography (PET), ¹⁸F-fluorodeoxyglucose (¹⁸F-FDG) ¹⁸F-flourodihydroxyphenylalanine PET. (¹⁸FDOPA) PET, and ¹¹C-hydroxy-ephedrine (HED) PET. MIBG is a norepinephrine analogue accumulated in the adrenal medulla and tumors originating from chromaffin tissue. MIBG labeled with ¹²³I is used for detection and staging of PPGLs. The sensitivity for ¹²³I-MIBG scintigraphy is between 28% and 100% (38-41). It is higher for pheochromocytomas (85-88%) and lower for paragangliomas (56-75%) (35). The specificity ranges between 70% and 100% (35, 38). In SDHx mutation carriers, however, the sensitivity of ¹²³I-MIBG scintigraphy is lower than for other imaging methods, especially in patients with thoracic paragangliomas (sensitivity 30.8% for ¹²³I-MIBG scintigraphy compared with 61.5% for somatostatin receptor scintigraphy and 46.2% for CT scan), which was shown in a large prospective multicenter study (42). The degree of FDG uptake in PPGLs is dependent on

Figure 1. CT scan with contrast enhancement, arterial phase, of a patient with metastatic pheochromocytoma.

the differentiation of the tumor. Pheochromocytomas usually have increased, yet often variable, FDG uptake, and the usefulness of this method is limited by the low specificity (35). Sensitivity and specificity of HED PET for diagnosis of pheochromocytomas and paragangliomas is reported to be 96% and 93% to 99%, respectively, with positive and negative predictive value of 96% and 93% to 99%, respectively (43). HED PET is, however, not universally available. A majority of PPGLs express somatostatin receptors. Previously, indium-111 octreotide scintigraphy (Octreoscan) was used for detection of PPGLs and other neuroendocrine tumors, but this imaging method has now been replaced by PET with ⁶⁸Ga-labeled DOTATOC or DOTATATE targeting mainly somatostatin receptor 2, due to its much higher sensitivity. The efficacy of ⁶⁸Ga-labeled DOTATOC or DOTATATE in localizing metastatic PPGLs has been demonstrated by several authors, showing sensitivity between 92% and 100% (39, 41, 44-50), which is higher than for the other imaging





Figure 2. ¹²³I-MIBG scintigraphy of the same patient as in Fig. 1.The metastases are clearly MIBG avid.



Figure 3. $^{68}\mbox{Ga-DOTATOC}$ PET CT scintigraphy of the same patient as in Figs. 1 and 2.The metastases show intense DOTATOC uptake.

methods. One study, however, found higher per-patient detection rate for ¹⁸FDOPA PET, yet the per-lesion detection rate was higher for ⁶⁸Ga-DOTATATE PET (48). The sensitivities for various imaging methods are shown in Table 1. In the most recent guidelines from European Association of Nuclear Medicine (EANM), ¹⁸FDOPA PET is recommended as the first choice in patients with sporadic and inherited pheochromocytomas (NF1, RET, VHL, MAX) except SDHx, and ⁶⁸Ga-DOTATOC/DOTATATE PET is recommended as first choice in extra-adrenal sympathetic and/or multifocal and/or metastatic and/or SDHx mutation. Second choice in sporadic and inherited pheochromocytomas is ⁶⁸Ga-DOTATOC/DOTATATE PET and third choice is ¹⁸F-FDG PET. In metastatic PPGL, ⁶⁸Ga-DOTATOC/DOTATATE PET is first choice, ¹⁸FDOPA PET may be used as second-line in patients with no known SDHB mutation, ¹⁸F-FDG PET as second-line in patients with SDHB mutation and ¹²³I-MIBG scintigraphy to determine whether the patient is suitable for ¹³¹I-MIBG therapy (51).

Pathology and Genetics

Despite the rather high accuracy of biochemical and imaging analyses in pinpointing PPGLs in the clinical setting, pathology remains the gold standard for diagnostic purposes (52). While fine needle aspiration and core needle biopsies are useful for diagnostic purposes of metastatic lesions (Fig. 4), it can be dangerous and is generally not used preoperatively to verify the suspicion of a primary PPGL due to the potential risk of an iatrogenic hypertensive crisis (53). Instead, a postoperative histological analysis of the resected specimen is standard practice. PPGLs are often well-circumscribed lesions, and the tumors commonly present with classic architecture in the form of alveolar-patterned cell nests (traditionally referred to as "zellballen") against a well-vascularized stroma (52). The tumor cell nuclei display a vesicular chromatin and visible nucleoli, and the cytoplasm is often granular and intensely basophilic. The tumors invariably express neuroendocrine markers such as chromogranin A, synaptophysin, ISLET1, and INSM1 (54) and are most often keratin-negative and GATA3-positive, with few exceptions (55). From a differential diagnosis perspective, when the surgical pathologist assesses core needle biopsies from apparent metastatic deposits, the combination of tumoral positivity for neuroendocrine markers and GATA3 with negative keratin stains strongly argues in favor of metastatic PPGL and basically excludes most well-differentiated neuroendocrine tumors of the gastrointestinal tract.

PPGLs are considered the most heritable of all tumors, with a veritable smorgasbord of gene candidates—around

Imaging modality	Sensitivity	Author	
CT/MRI	93% patient-based	Archier 2016 (48)	
	76% lesion-based		
CT/MRI	81.6% lesion-based	Janssen 2016 (45)	
CT/MRI	90.9% lesion-based	Jha 2018 (50)	
¹⁸ F-FDG	91.4% lesion-based	Chang 2016 (39)	
¹⁸ F-FDG	49.2% lesion-based	Janssen 2016 (45)	
¹⁸ F-FDG	89% primary tumor	Jing 2017 (40)	
¹⁸ F-FDG	90.9% lesion-based	Jha 2018 (50)	
¹⁸ F-FDG	85%	Kan 2018 (46)	
¹⁸ F-FDG	74%	Han 2019 (44)	
¹⁸ FDOPA	97% patient-based	Archier 2016 (48)	
	89% lesion-based		
¹⁸ FDOPA	74.8% lesion-based	Janssen 2016 (45)	
¹⁸ FDOPA	80%	Han 2019 (44)	
¹⁸ FDOPA	82.3% lesion-based	Kroiss 2019 (47)	
⁶⁸ Ga-DOTATATE	96% lesion-based	Naji 2011 (41)	
⁶⁸ Ga-DOTATATE	93% patient-based	Archier 2016 (48)	
	93% lesion-based		
⁶⁸ Ga-DOTATATE	96.2% lesion-based	Chang 2016 (39)	
⁶⁸ Ga-DOTATATE	97.6% lesion-based	Janssen 2016 (45)	
⁶⁸ Ga-DOTATATE	100% primary tumor	Jing 2017 (40)	
⁶⁸ Ga-DOTATATE	88% PCC, 100% PGL	Gild 2018 (49)	
⁶⁸ Ga-DOTATATE	93.5% lesion-based	Jha 2018 (50)	
⁶⁸ Ga-DOTATOC/DOTATATE	95%	Kan 2018 (46)	
⁶⁸ Ga-DOTATOC/DOTATATE	93% (92%-100%)	Han 2019 (44)	
⁶⁸ Ga-DOTATOC	100% lesion-based	Kroiss 2019 (47)	
¹²³ I-MIBG	28% lesion-based	Naji 2011 (41)	
^{123/124} I-MIBG	30.4% lesion-based	Chang 2016 (39)	
¹²³ I-MIBG	100% primary tumor	Jing 2017 (40)	
¹²³ I-MIBG	85%-88% PCC, 56%-75% PGL	Ctvrtlik 2018 (35)	
^{123/131} I-MIBG	38%	Han 2019 (44)	
¹²³ I-MIBG	75%-95%	Itani 2019 (38)	

Table 1. Sensitivities for Varying Imaging Modalities in Patients With Pheochromocytomas and Paragangliomas: HighestSensitivity is Obtained with 68 Ga-DOTATATE/DOTATOC PET CT

Abbreviations: PCC, pheochromocytomas; PGL, paragangliomas.

20 PPGL susceptibility genes with germline mutations in patients with PPGL have been detected to date (56). As of this writing, it is now recommended that all patients with PPGL are referred for clinical genetic consultation. Since there currently are no definite prognostic markers that accurately predict malignant behavior in primary tumors, the updated 2017 version of the WHO classification tried to tackle the "benign vs malignant" PPGL dilemma with the introduction of the terminology "non-metastatic" and "metastatic," respectively, in which a metastatic PPGL is defined as such if the location is normally devoid of normal chromaffin cells.

Nowadays, all PPGLs are believed to carry a malignant potential, and the surgical pathologist is therefore mandated to stratify this risk using histological attributes as a guideline. We know that PPGLs displaying invasive behavior (vascular invasion, capsular invasion, and/or extension into

the surrounding fat), along with bizarre histological architecture (irregular cell nests) and cytological attributes (aggravated pleomorphism, spindle cells, high mitotic counts and so on), are overrepresented among cases that will subsequently metastasize, even many years after the initial surgical resection—but even so, these histological attributes are not seldom seen also in cases with a benign course. As of this, histological algorithms with a structured scoring system have been put forward as useful in predicting aggressive biological behavior, of which the Pheochromocytoma of the Adrenal Gland Scaled Score (PASS) and the Grading System for Adrenal Pheochromocytoma and Paraganglioma (GAPP) systems are the most frequently used (57, 58). The former system was originally designed for pheochromocytomas and incorporates 12 histological attributes that are often overrepresented in metastatic cases. The score generated ranges from 0 to 20, and a score of \geq 4 points pinpoints cases



Figure 4. Histological and immunophenotypic profile of a metastatic pheochromocytoma. Top row: Hematoxylin-eosin stains of a core needle biopsy of a pheochromocytoma metastatic to the liver. Note the nested growth pattern, the monomorphic nuclei and the well-vascularized stroma. Middle-bottom rows: Immunohistochemical analyses pinpointed immunoreactivity for **A**, chromogranin A; **B**, synaptophysin; **C**, ISL1; and **D**, GATA3. Pan-cytokeratins (E) were negative (with hepatocytes to the left as internal controls), and SDHB expression was intact (granular cytoplasmic staining) (F). All photomicrographs were magnified x400, apart from the low power magnification of the core needle biopsy in the upper left corner (at x100). Abbreviations: H&E; hematoxylin-eosin stain, IHC; immunohistochemistry.

at risk of future aggressive behavior. Although criticized for its somewhat subpar reproducibility, a recent meta-analysis verified a rather high negative predictive value of the method in which a case with a PASS score of <4 almost always is associated to a benign clinical course (59). The GAPP algorithm, designed for both pheochromocytomas and abdominal paragangliomas, expands on the PASS system by also including biochemical (type of catecholamine production) and immunohistochemical (Ki-67 proliferation index) analyses, thereby stratifying the PPGLs into 3 different classes with significant associations to patient outcome. Although a younger algorithm with fewer verification studies available, the GAPP score was also shown to exhibit a strong rule-out function given its high negative predictive value (59).

As the current histological concepts thus seem to focus on ruling out the risk of future recurrences, it comes to no surprise that clinicians and researchers turn to molecular genetics for additional clues to rule-in cases at imminent risk of metastatic spread. Traditionally, PPGLs were divided into 2 main expressional clusters when profiling the messenger RNA (mRNA) patterns of these tumors: a hypoxiarelated cluster (cluster 1) and a kinase-driven cluster (cluster 2) (60), with the subsequent addition of a third and fourth cluster with overexpression of Wingless type (Wnt) signaling pathway genes and adrenocortical genes respectively (61, 62). Cluster 1 PPGLs display a pattern of

mRNAs related to pathways associated to hypoxia, and tumors in this cluster often display mutations in VHL as well as members of the SDHx gene family (most notably SDHB and SDHD), while cluster 2 PPGLs are enriched for cases with mutations in RET, NF1, and HRAS, to name a few (61). Notably, cluster 1 PPGLs are overrepresented among metastatic cases, and therefore tumors with this mRNA expressional pattern could be considered high-risk cases as compared with kinase cluster PPGLs. However, as multigene expressional profiling is cumbersome and expensive from a clinical standpoint, analyses of individual molecular aberrancies have gained ground as predictors of future metastatic spread. The most notable predictor of aggressive clinical behavior is the presence of a germline SDHB mutation, as these mutations predispose the familial paraganglioma-pheochromocytoma syndrome PLG4, which is tightly coupled to the development of abdominal paragangliomas that are often metastatic (63, 64). For this reason, SDHB immunohistochemistry has proven a valuable tool to triage cases for genetic testing (65). In addition to SDH gene family mutations, other members of the Krebs cycle and/or mitochondrial metabolism have also been implicated in the development of PPGLs, of which several have proven metastatic, including germline mutations in the mitochondrial 2-oxoglutarate/malate carrier SLC25A11 (66), the glutamic-oxaloacetic transaminase

2 (GOT2) gene (67) as well as the dihydrolipoamide S-succinyltransferase (DLST) gene (68). In all, these findings provide a strong link between mutations in Krebs cycle related genes and metastatic properties of PPGLs, and mitochondrial pathways could potentially constitute a platform for future therapeutic targets. For example, PPGLs exhibiting SDHx gene mutations and a deficient succinate dehydrogenase enzyme will accumulate succinate, in turn leading to inhibition of various DNA demethylases and the acquired hypermethylation of tumor DNA (69). As O-6methylguanine-DNA methyltransferase (MGMT) is one of the epigenetically silenced genes in SDHx mutated PPGLs, this could probably explain the partial response in SDHx mutated PPGL patients using temozolomide (70). Moreover, SDHB-mutated PPGLs have also been shown to acquire the above-mentioned hypermethylation phenotype via inhibition of ten-eleven translocation (TET) expression (71). As TET enzymes play a central role in DNA demethylation processes, the diminished enzymatic activity would in theory help to upkeep tumor DNA hypermethylation. Interestingly, while TET inhibition alone was insufficient to drive PPGL cells into an invasive phenotype in functional experiments, the synergistic activation of HIF2 α facilitated the acquisition of metastatic traits-thereby opening up for future potential therapeutic strategies targeting the HIF-TET axis in clinical studies (71).

Other, nonmitochondrial related genetic aberrances coupled to metastatic PPGLs include *MAML3* fusions, somatic mutations in *SETD2* and *ATRX*, as well as *TERT* promoter structural variants and noncoding mutations (61, 72-74). Moreover, expression of chromogranin B was recently coupled to high PASS scores and adverse clinical events in a series of PPGLs, and the results were also reproduced in preoperative plasma levels, suggestive of a noninvasive marker to appreciate the metastatic potential of these enigmatic tumors (75).

Treatment

Since most PPGLs are nonmetastatic, surgical treatment is curative (1, 76). Surgery may also be an option in patients with PPGLs that have metastasized only to regional lymph nodes. In addition, 2 studies have demonstrated improved survival for patients with distant metastases undergoing surgical removal of the primary tumor compared with patients not having their primary tumor removed (77, 78). In cases with localized recurrence, repeated surgery may be performed. Pre- and perioperative alpha-receptor blockade as well as correction of intravascular volume is essential to avoid hypertensive crises and hypotension during surgery (76). The most frequent drugs used are phenoxybenzamine, a nonselective and noncompetitive alpha-1 and alpha-2 adrenergic receptor blocker, and doxazosin, a selective and competitive alpha-1 adrenergic receptor blocker. Phenoxybenzamine may be taken once daily, but doxazosin needs to be administered 2 or 3 times daily since it may be released from the alpha receptors in case of a sudden catecholamine release from the tumor. One of these drugs should be commenced 1 to 2 weeks prior to surgery with increased dosages until the blood pressure targets have been achieved (2, 76, 79). Some centers have used longer pretreatment periods before surgery (17). There is no consensus on which of the 2 drugs to use, some prefer doxazosin due to its wider availability and less adverse effects. In the only randomized control trial so far, no difference in the duration of blood pressure outside the target range during surgery was found when comparing pretreatment with doxazosin and phenoxybenzamine (80). However, patients using phenoxybenzamine less frequently had intraoperative systolic blood pressure above the target range and hemodynamic instability. The intravenous alphablocker phentolamine is preferred in emergency situations, such as PPGL-crisis, due to its quick onset (25). Calcium channel blockers (nifedipine or amlodipine) normally are used as an addition to alpha adrenergic receptor blocker if further blood pressure control is required or occasionally for patients not tolerating alpha-blockers (76, 79). In contrast, beta-blockers are used to control tachycardia. However, it is essential that alpha-blockers are commenced first to avoid potential PPGL-crisis since beta-blockers alone may aggravate epinephrine-induced vasoconstriction by blocking its vasodilator component, ie, unopposed alpha-receptor stimulation (25, 79). Propranolol, metoprolol, or atenolol are commonly used beta-blockers. Both beta-1 selective blockers and nonselective beta-blockers are equally good (76). Labetalol, which is a more potent betathan alpha-blocker, should be avoided (1). In cases with widespread metastatic disease, the therapeutic possibilities are more limited, and the prognosis is worse. The options are chemotherapy, radionuclide treatment, and the newer targeted therapies. Effective hypertension therapy in metastatic PPGL has not been established but practically should follow the principles above (79). In order to avoid severe hypertensive crises, it is recommended that all patients with metastatic hormone-secreting PPGLs receive at least a low dose of an alpha-blocking agent. Metyrosine (alphamethylthyrosine), which inhibits the enzyme thyrosine hydroxylase and thereby depletes the levels of epinephrine, norepinephrine, and dopamine, markedly reduced catecholamine secretion in up to 1 in 4 of those using it for chronic treatment (81); however, nowadays it is not often used in clinical practice.

A rare symptom in patients with PPGLs is constipation, which may be associated with headache, palpitations, diaphoresis, weight loss, and high noradrenaline levels. Treatment with water, fiber, and laxatives may lead to symptom improvement (82).

Chemotherapy

The mainstay treatment of metastatic PPGLs has previously been chemotherapy. A combination of cyclophosphamide, vincristine, and dacarbazine has shown efficacy in 2 studies. Averbuch et al treated 14 patients with cyclophosphamide 750 mg/m² day 1, vincristine 1.4 mg/m² day 1, and dacarbazine 600 mg/m² day 1 and 2, every 21 days (83). Complete and partial objective responses were obtained in 57% of patients, with median response duration of 21 months. Biochemical response was seen in 79% of patients (83). In another study, 18 patients were treated with cyclophosphamide 750 mg/m² day 1, vincristine 1.4 mg/m² day 1, and dacarbazine 600 mg/m² day 1 and 2, every 21 to 28 days; the complete response (CR) rate was 11% and partial response (PR) rate was 44% (84). Median survival was 3.8 years for responders and 1.8 years for nonresponders. The chemotherapy was well tolerated, with only grade I to II toxicities observed. All patients whose tumors responded had symptom improvement. The same regimen was used in another study encompassing 12 patients with metastatic SDHB-mutated paragangliomas (85). Median 20.5 cycles (range, 4-41) were administered. All patients experienced tumor reduction (12%-100%). Two patients had CR, 8 had PR, and 2 had minor response according to response evaluation criteria in solid tumors (RECIST) criteria. Median response duration was 1.3 years, median progression-free survival (PFS) 2.5 years and median overall survival was 3.3 years. There was a continuous reduction in maximal standardized uptake values (SUV_{max}) in 26/30 lesions (87%) on 18 F-FDG PET.

Temozolomide is an orally administered drug that shares its active metabolite with dacarbazine. It is used in neuroendocrine tumors, both as monotherapy and in combination with capecitabine (86-89). Several case reports have demonstrated that temozolomide also may be active in metastatic PPGLs (90, 91). In a consecutive retrospective study, 15 patients with PPGLs, among whom 10 (67%) had *SDHB* mutation, were treated with temozolomide (median dose 172 mg/ m²) daily for 5 days every 28 days (70). Median PFS was 13.2 months. Five patients (33%) had PR, 7 patients (47%) had stable disease, and 3 patients (20%) progressed. Partial response was only seen in patients with *SDHB* mutation.

Radionuclide Treatment

¹³¹I-MIBG

The norepinephrine analogue MIBG labeled with iodine-131 (¹³¹I-MIBG), a beta-emitter and gamma-emitter

with a half-life of 8 days, has been used for more than 2 decades for treatment of PPGLs and other neuroendocrine tumors. The antitumoral activity has been demonstrated by several authors. Complete or partial radiological responses have been observed in 10% to 34% of patients, and disease control (CR + PR + stable disease) in 30% to 92% of patients. Loh et al reported on 116 patients treated with a mean 3.2 (range, 1–11) cycles of ¹³¹I-MIBG (92). The mean single dose was 5.8 GBq (158 mCi) and mean cumulative dose was 18.1 GBq (range, 3.6-85.9 GBq; 490 mCi range, 96-2322 mCi). Objective tumor response was seen in 30% of patients, of whom 5 had CR during 16 to 58 months, hormonal response was observed in 45%, and symptomatic improvement in 76%. Adverse effects, affecting 41% of treated patients, were generally mild, apart from 1 patient who died from bone marrow aplasia. Gonias et al treated 50 patients harboring metastatic PPGLs with ¹³¹I-MIBG doses ranging between 492 and 1160 mCi, cumulative doses ranging between 492 and 3191 mCi with filgrastim and stem cell support (93). Overall CR plus PR rate in 49 evaluable patients was 22%, and an additional 43% had stable disease (35% of whom had response in one measure). Overall 5-year survival was 64%. Two patients developed myelodysplastic syndrome. Since >99% of the MIBG molecules in commercially available ¹³¹I-MIBG are not radiolabeled (94, 95), high-specific-activity ¹³¹I-MIBG (iobenguane ¹³¹I) with little or no unlabeled MIBG, has been produced by a process named Ultratrace. This drug has the same tissue distribution in nontarget tissue but much higher uptake in PPGLs (96). In a phase 1 study of 21 patients treated with high-specific-activity ¹³¹I-MIBG, 4 patients (19%), all of whom received >18.5 GBq, had PR according to RECIST. Overall 2-year survival was 62%. Adverse effects were mild or moderate (95). In another study, high-specific-activity ¹³¹I-MIBG was administered to 68 patients, 49 with pheochromocytoma and 19 with paraganglioma, all metastatic, who received 1 (19 patients) or 2 doses (50 patients) of 18.5 GBq (500 mCi); in 1 patient, the dose was reduced to 3.8 GBq (102 mCi) due to high tumor burden (97). The median cumulative ¹³¹I-MIBG dose was 35.7 GBq (range, 3.8-40.5 GBq; or 965 mCi, range, 102-1096 mCi). In 64 patients, evaluable for objective response, 15 patients (23%) had PR and 44 patients (69%) had stable disease. In the 50 patients who received 2 doses, 15 (30%) had PR. Median overall survival was 37 months (44 months for those who received 2 treatments), and the 1-year, 2-year, 3-year and 5-year overall survival rates were 91%, 72%, 52%, and 36%, respectively. Myelodysplastic syndrome occurred in 3 patients (4%), and acute myeloid leukemia and acute lymphocytic leukemia occurred in 1 patient (1%) each. A Japanese study evaluated 20 patients with metastatic PPGLs receiving fixed ¹³¹I-MIBG doses of 5.55 or 7.4 GBq (98). Nine patients received 1

dose, 8 patients received 2 doses, and 3 patients received 3 doses. Best response according to RECIST criteria was 10% CR, 65% stable disease, and 15% progressive disease. In a recent, long-term follow-up of 125 patients with metastatic PPGLs progressing on prior therapies, who were treated with median 18.8 GBq ¹³¹I-MIBG, median survival from post therapy was 4.3 years. Among 88 patients with follow-up imaging, 1% had CR, 33% had PR, 53% had stable disease, and 13% progressed (99). Subsequent progression was seen on 51%. Median PFS was 2.0 years and median overall survival was 11.5 years from diagnosis and 4.3 years from start of treatment.

¹⁷⁷Lutetium-DOTATATE, ⁹⁰Yttrium-DOTATOC

A majority of neuroendocrine tumors express somatostatin receptors, making it possible to treat these patients with radiolabeled somatostatin analogues. Lutetium-177 (177Lu) and Yttrium-90 (90Y) emit beta particles; 177Lu in addition emits gamma rays. 177Lu-DOTATATE has been used for 20 years to treat patients with gastroenteropancreatic and other neuroendocrine tumors. The results are promising, with objective response rates up to 39%, disease control rates up to 92%, and PFS up to 33 months (100, 101). Among 28 patients with inoperable PPGLs, 25 received in total 200 mCI/m² ⁹⁰Y-DOTATOC and 3 patients received 1 cycle with 100 mCi/m^{2 90}Y-DOTATOC followed by 2 cycles of 200 mCi/ m²¹⁷⁷Lu-DOTATOC (102). The result was 2 PR, 5 minor responses, 13 stable disease, 2 mixed responses, and 6 progressive disease. Time to progression was 3 to >42 months. Another early report of 12 patients with PPGLs, 4 of whom were progressing, treated with a cumulative dose of 22.2-29.6 GBq ¹⁷⁷Lu-DOTATATE, found 2 PR, 6 stable disease, and 3 patients progressing (103). A more recent study from the same group encompassed 30 patients with inoperable or metastatic PPGLs, who were treated with up to 4 cycles of 7.4 GBq ¹⁷⁷Lu-DOTATATE (104). PR was seen in 7 (23%), stable disease in 20 (67%), and progressive disease in 3 (10%). Tumor control was achieved in 17/20 (85%) with progression on inclusion. Median PFS was 91 months in patients with parasympathetic paragangliomas, 13 months in patients with sympathetic paragangliomas, and 10 months in patients with metastatic pheochromocytomas. Kong et al reviewed 20 patients with high somatostatin receptor expression treated with median 4 cycles of ¹⁷⁷Lu-DOTATATE (mean cumulative activity 22 GBq), 9 of whom in addition received radiosensitizing chemotherapy (105). Radiological regression was seen in 38% (29% PR, 7% minor response) and stable disease in 50%. Median PFS was 39 months. Concomitant ¹⁷⁷Lu-DOTATATE and capecitabine was used in another observational study of 25 patients with paragangliomas, who received an average dose of

22.86 (range, 14.43-50) GBq ¹⁷⁷Lu-DOTATATE combined with capecitabine 1250 mg/m² days 1 to 14 (106). Radiological response according to RECIST 1.1 criteria occurred in 7/25 patients (28%) and median PFS was 32 months. The Uppsala group reported 22 patients with PPGLs, of whom 20 had metastatic and 2 had localized disease, receiving median 4 cycles (range, 3-11) with 7.4 GBq¹⁷⁷Lu-DOTATATE (107). Nine patients were treated because of progressive disease and 13 as first-line therapy. PR was attained in 2 (9%) and stable disease in 20 patients (91%). Median PFS was 21.6 (6.7-138) months and median overall survival was 49.6 (8.2-139) months. Patients receiving ¹⁷⁷Lu-DOTATATE as first-line therapy had better overall survival than those treated because of progressive disease. In a meta-analysis including 12 studies, in total encompassing 201 patients with advanced PPGLs treated with ¹⁷⁷Lu-DOTATATE or ⁹⁰Y-DOTATOC, the overall objective response rate was 25% (19%-32%) and disease control rate was 84% (77%-89%) (108). Biochemical response occurred in 64% and clinical response in 61%. There was no difference in response between those treated with ¹⁷⁷Lu-DOTATATE or ⁹⁰Y-DOTATOC. Adverse effects were mild.

There are few studies comparing treatment with ¹³¹I-MIBG and ¹⁷⁷Lu- or ⁹⁰Y-labeled radiopeptides (peptide receptor radionuclide therapy; PRRT) in patients with PPGL. In a recent report, 22 patients with progressive and/ or metastatic PPGLs received a total of 30 treatments with either ¹³¹I-MIBG (n = 16), ¹⁷⁷Lu-DOTATATE (n = 2), or ⁹⁰Y-DOTATATE (n = 12). Response to treatment and PFS was significantly better for patients treated with PRRT, but there was no difference in overall survival for the whole group. Patients with PPGL treated with PRRT, however, had better overall survival than those receiving ¹³¹I-MIBG (109).

Other Medications

Tyrosine kinase inhibitors

Sunitinib, an inhibitor of vascular endothelial growth factors 1 and 2 (VEGFR-1, VEGFR-2), platelet-derived growth factor- β , c-KIT, FLT3, and RET, has been tried in a limited number of patients. Joshua et al reported 3 patients with metastatic paragangliomas treated with sunitinib 50 mg daily, 4 weeks on/2 weeks off (110). One patient had a near CR and 2 patients had PR. In another retrospective study of 17 patients with rapidly progressive PPGLs, 3 had PR and 5 had stable disease, including 4 with predominant bone metastases who had \geq 30% reduction in glucose uptake on ¹⁸F-FDG PET CT. Six patients progressed, and 3 could not be evaluated since sunitinib was stopped due to early toxicity (111). Median PFS was 4.1 months and median overall survival was 26.7 months from the start of therapy. Normalization of hypertension occurred in 6/14 patients

(42%). In a more recent report, 25 patients with PPGL (23 of whom had metastatic disease and 2 with locally advanced disease) were treated with sunitinib 50 mg daily 4 weeks on/2 weeks off, 23 of whom were evaluable for response. Partial response was obtained in 3 patients (13%) and 16 (70%) had stable disease; hence, the disease control rate was 83%. The median PFS was 13.4 months (112). An ongoing trial, the FIRSTMAPP study, is evaluating sunitinib 37.5 mg daily vs placebo in patients with progressing PPGL (113). The results are awaited with interest. Regarding sorafenib, another multitarget kinase inhibitor, there are only case reports and no clinical studies; hence, the efficacy needs to be evaluated in more comprehensive studies (114). Other tyrosine kinase inhibitors, including cabozantinib, lenvatinib, and axitinib, are currently being tested in active and/or recruiting clinical trials (www. ClinicalTrials.gov), the results of which are not yet available or only very preliminary (115).

mTOR inhibitors

Everolimus is an inhibitor of the PDK/AKT/mTOR signal pathway, which regulates cell proliferation, apoptosis, and angiogenesis. Two small reports have yielded conflicting results about the efficacy of everolimus in patients with PPGLs (116, 117).

Immune checkpoint inhibitors

Pembrolizumab is a humanized monoclonal antibody targeting the programmed cell death (PD1)/programmed cell death ligand (PDL-1) pathway. It binds to the PD1 receptor and thereby block its interaction with the ligands PDL-1 and PDL-2, leading to a potentiation of the T-cell immune response, including the antitumoral response. In a large study of pembrolizumab in patients with rare cancers, including 9 with PPGLs, the nonprogressing rate at 27 weeks was 43% (3/7 evaluable patients) (118). At the time of data cutoff, 6/8 patients had stable disease according to immune-related RECIST (irRECIST) criteria. Jimenez et al reported 11 patients with metastatic PPGLs treated with pembrolizumab (119). The objective response rate according to irRECIST was 9% PR, 64% stable disease (including 3 patients with some degree of regression); hence, 73% of patients had clinical benefit. PFS at 27 weeks was 40% and median survival was 19 months. Positive response was independent of PDL-1 expression in primary tumor.

Somatostatin analogues

There are 2 somatostatin analogues targeting mainly somatostatin receptor 2 but also somatostatin receptor 5, octreotide and lanreotide, available in long-acting formulations. Two studies have shown antitumoral activity of octreotide LAR (120) and lanreotide Autogel (121) in patients with low-proliferative gastroenteropancreatic neuroendocrine tumors. Apart from the antitumoral activity, these drugs may also lower hormone secretion, leading to amelioration of distressing endocrine symptoms, such as the carcinoid syndrome. There are, however, no randomized trials of treatment with somatostatin analogues in patients with PPGLs. Nevertheless, since a majority of PPGLs express somatostatin receptors (39, 44) and PPGLs have responded well to PRRT, treatment with somatostatin analogues seems interesting in these patients. In a case report, a woman with an ACTHsecreting pheochromocytoma resulting in Cushing syndrome responded biochemically to octreotide with a reduction of ACTH and serum cortisol (122).

Local Ablative Treatment

Ablative treatment of metastases includes radiofrequency ablation, cryoablation, and percutaneous ethanol injection (123). In a retrospective study of 31 patients with metastatic PPGL, 123 lesions were treated with ablative therapy during 42 radiofrequency ablation procedures, 23 cryoablation procedures, and 4 percutaneous ethanol injection procedures. Radiologic evaluation was performed of 80 lesions. Local control was achieved in 69 (86%) of these lesions. Improvement in symptoms (pain or catecholaminerelated symptoms) was obtained after 12/13 (92%) procedures (124). In another study, interventional radiology techniques (cementoplasty, osteosynthesis, thermal ablation) delayed time to first serious skeletal-related event in patients with PPGL harboring bone metastases (125). External beam radiation may also be used for local control and symptom palliation. In one study including 41 patients with 107 treated sites, local control at 5 years was achieved in 81% of treated lesions. All 11 lesions treated with stereotactic radiotherapy or radiosurgery exhibited local control at a median 3 years (126).

Antiresorptive therapy

Bone metastases occur in about 70% to 80% of patients with PPGL, leading to severe pain, spinal cord compression, and pathologic fractures (113). Treatment with bisphosphonates or denosumab is recommended for all patients with PPGL and bone metastases in order to decrease the frequency of skeletal-related events (127, 128).

Conclusions

To pinpoint metastatic potential in PPGLs is difficult, but nevertheless crucial for the individual patient to receive tailor-made follow-up and adjuvant treatment following primary surgery. A combination of histological workup and molecular predictive markers can possibly aid the clinicians in this aspect. A majority of patients with pheochromocytoma have localized disease and may be cured by surgery, while a larger proportion of abdominal paragangliomas are metastatic at the time of diagnosis. Plasma metanephrines, 3-methoxytyramine, as well as chromogranin A, are the main biochemical tests. Genetic testing is important, both for counseling and prognostic estimation. Apart from CT and MRI, molecular imaging with ⁶⁸Ga-DOTATOC/ DOTATATE PET or ¹⁸FDOPA PET should be performed. ¹²³I-MIBG scintigraphy may be used to determine whether the patient is eligible for therapy with ¹³¹I-MIBG. There are several treatment possibilities (Table 2). Since a substantial number of metastatic PPGLs are slow-growing, show an indolent course, and are associated with a good quality of life, one option may be to "wait and see," under close surveillance. As first-line treatment in patients with progressing metastatic PPGLs, ¹⁷⁷Lu-DOTATATE or ¹³¹I-MIBG is recommended, depending on which shows best expression.

Table 2.	Recommended	First-Line	Treatment for	Patients With	Metastatic	Pheochromocvton	nas and Paragangliomas

Avidity	Treatment
⁶⁸ Ga avid, ¹²³ I-MIBG avid	¹⁷⁷ Lu-DOTATATE and/or ¹³¹ I-MIBG depending on uptake intensity
⁶⁸ Ga avid, ¹²³ I-MIBG non-avid	¹⁷⁷ Lu-DOTATATE
⁶⁸ Ga non-avid, ¹²³ I-MIBG-avid	¹³¹ I-MIBG
⁶⁸ Ga non-avid, ¹²³ I-MIBG non-avid	
Low proliferative activity	Temozolomide
High proliferative activity	Cyclophosphamide + vincristine + dacarbazine

Patients who respond to or are stable on first-line treatment with ¹⁷⁷Lu-DOTATATE and/or ¹³¹I-MIBG, but later show progression may receive repeated radionuclide therapy. If the progression occurs during the first year after finishing radionuclide therapy, chemotherapy is suggested instead. In patients with high proliferative activity, chemotherapy is first-line regardless of DOTATOC or MIBG avidity. In patients with very low proliferative activity, positive on ⁶⁸Ga-DOTATOC PET, primary treatment with somatostatin analogues may be considered. Tyrosine kinase inhibitors, somatostatin analogues, sunitinib, and cabozantinib are sometimes used but are not first-line treatment.

Treatment	N/E	CR + PR	SD	DCR	PFS	Reference
CVD	14	57%				Averbuch (83)
CVD	18	55%				Huang (84)
CVD	12	83%			2.5 y	Jawed (85)
Temozolomide	15	33%	47%	80%	13.2 mo	Hadoux (70)
¹³¹ I-MIBG	116	30%				Loh (92)
¹³¹ I-MIBG	50/49	22%	43%	65%		Gonias (93)
HS- ¹³¹ I-MIBG	21	19%				Noto (95)
HS- ¹³¹ I-MIBG	68/64	23%	69%	92%		Pryma (97)
¹³¹ I-MIBG	20	10%	65%	75%		Wakbayashi (98)
¹³¹ I-MIBG	125/88	34%	53%	87%		Thorpe (99)
¹⁷⁷ Lu-DOTATATE	12/11	2	6			van Essen (103)
90Y-DOTATOC	28	2 (7%)	18 (64%)	20 (71%)		Forrer (102)
¹⁷⁷ Lu-DOTATATE	30	23%	67%	90%	13* mo / 10 [#] mo	Zandee (104)
¹⁷⁷ Lu-DOTATATE	20	29%	57%	88%	39 mo	Kong (105)
¹⁷⁷ Lu-DOTATATE	22	2 (9%)	20 (91%)		21.6 mo	Vyakaaranam (107)
¹⁷⁷ Lu, ⁹⁰ Y	201	25%				Satapathy (108)
Everolimus	7	5	5			Oh (117)
Sunitinib	25	13%	70%	83%	13.4 mo	O'Kane (112)
Sunitinib	17/14	3	5		4.1 mo	Ayala-Ramirez (111)
Pembrolizumab	9/8	6	6			Naing (118)
Pembrolizumab	11	1 = 9%	7 (64%)	8 (73%)	5.7 mo	Jimenez (119)

Table 3. Studies Showing the Effects of Various Treatments for Patients With Metastatic Pheochromocytomas and

 Paragangliomas

Abbreviations: CVD, cyclophosphamide + vincristine + dacarbazine; CR, complete response; DCR, disease control rate; E, evaluable; PFS, progression-free survival; PR, partial response; SD, stable disease.

*PGL

#pheo

For abdominal PPGLs/metastatic PPGLs, DOTATATE therapy seems to be more effective. In patients with very low proliferative activity, watch-and-wait or primary treatment with long-acting somatostatin analogues may be considered. Suggested first-line treatment of patients with metastatic PPGLs is shown in Table 2, and the effects and numbers of patients in the respective studies are shown in Table 3. As second-line treatment, or first-line in patients with high proliferative rate, chemotherapy with temozolomide or cyclophosphamide + vincristine + dacarbazine is the therapy of choice. Other therapies, including sunitinib, cabozantinib, everolimus, and PD-1/PDL-1 inhibitors, have shown modest effect. Local ablative therapies, such as radiofrequency ablation, cryoablation, and percutaneous thermal ablation, may achieve local control or symptomatic relief in selected patients. Further studies and newer treatment modalities are urgently needed. New guidelines regarding the management and research opportunities of sporadic and hereditary PPGLs have recently been published (76, 129).

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