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Metastatic Paraganglioma

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Abstract

Paragangliomas (PGLs) are rare chromaffin cell tumors that can often be cured by resection. Although described for the first time in 1886 [1], the diagnosis of PGL remains a challenge, because patients do not present with characteristic signs and symptoms. If untreated, PGL can have a devastating outcome due to myocardial infarction, severe hypertension, stroke and/or arrhytmia caused by catecholamine excess. Even after proper diagnosis, the risk of metastatic disease remains. In recent years the opinion that metastatic disease is rare in PGL had to be revised, particularly in patients presenting with extra-adrenal PGL, with a PGL exceeding a size of 5 cm and/or carrying an *SDHB* germline mutation (especially for children and adolescents). In up to 10 % of patients, metastases are already present at diagnosis of PGL.

Measurement of plasma and urinary metanephrine levels has long been used effectively in the diagnosis of PGL. Recently, a dopaminergic phenotype (excess dopamine, L-3,4-dihydroxyphenylalanine and or methoxytyramine) was recognized as a good indicator for metastatic disease. Vast progress in targeted PET imaging (e.g. ^{18}F-FDA, ^{18}F-FDOPA, ^{18}F-FDG) now allows for reliable early detection of metastatic disease. However, once metastatses are present, treatment options are limited. Survival of patients with metastatic PGL is variable. Depending on the study population the overall 5 year survival is 35–60 %, [2].

Here we review recent advances involving findings about the genetic background, the molecular pathogenesis, new diagnostic indicators, pathologic markers and emerging treatment options for metastatic PGL.

Definition

Following the definition of the world health organization, paragangliomas (PGLs) are chromaffin cell tumors developing from the sympathetic and parasympathetic ganglia throughout the abdomen and head and neck area. A PGL arising from the adrenal gland is called pheochromocytoma (PHEO). In addition, here we will distinguish between

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[1]Carbidopa has been shown to increase the tumor-to-background ratio of ^{18}F-FDOPA uptake in PGL, particularly PHEO [68]

sympathetic extra-adrenal PGL (eaPGL) and parasympathetic PGL from the head and neck area (HNP). In general PGLs are well curable, however once a patient presents with metastases, treatment options are limited and rarely curative.

Metastatic disease due to PGL can only be diagnosed based on the presence of chromaffin tumors in locations where chromaffin cells are not usually present. Thus, the widely used term 'malignancy', that is spreading of a primary tumor by tissue and/or vascular invasion and/or metastazising, does not necessarily apply to PGL. While tissue and/or vascular invasion are sometimes observed in PGLs these observations don't correlate well with the severity of the disease and a patient's prognosis. Thus, in contrast to other malignancies, the development of metastases cannot be predicted or evaluated by high vascularization and mitotic rate, or vascular and/or tissue invasion. Despite huge efforts, currently no gene or protein has been identified as a definite marker or predictor for metastatic disease and no reliable cure has been developed yet.

Rule of 10 % Overcome

PGL has long been considered as the disease of 10 % (10 % metastatic, 10 % familial, 10 % recurring, 10 % extra-adrenal, 10 % occurring in children). However, improved diagnostic techniques showed that the rule of 10 % does not accurately characterize PGL. Overall, 0–36 % of PGL patients develop metastatic disease, depending on the type of tumor [3] (table 1). The percentage of PGL with family history has been revised to around 30 % [4, 5]. Extra-adrenal tumors have been reported in 15–20 % of patients [6].

Genetic Predispositions

Up to 30 % of PGL appear to present in a hereditary manner [4, 5]. To date, 8 different germline mutations are associated with PGL (*NF1*: van Recklinghausen Neurofibromatosis Type 1, *RET*: Multiple Endrocrine Neoplasia Type 2, *VHL*: von Hippel-Lindau disease, *SDH-B, -C, -D*: familial PGL syndrome 4, 3, 1, *SDH5* [7] (also referred to as *SDHAF1*): familial PGL syndrome 2, *TMEM127*: familial PGL, respectively). However, *SDH5*/*SDHAF1* mutation seems to be rare and should only be suspected in very young patients with HNP and family history thereof in absence of *SDHB, C* and *D* mutation [8]. *TMEM127* germline mutation seems to occur in up to 30 % of patients with other mutations predisposing to PGL. All PGL patients presenting with *TMEM127* germline mutation had PHEO. However, during follow up of 4–16 years none of the patients with *TMEM127* germline mutation developed metastases or recurrence [9]. In the majority of PGL the underlying dysfunction remains unknown and they are referred to as sporadic.

In search of additional genes that may be involved in the development of PGL, a somatic heterozygous mutation of isocitrate dehydrogenase has been reported in one patient with HNP, but was not found again in a large cohort of apparently sporadic PGL [10]. In addition, prolyl hydroxylase 2 (PHD2/EGLN1) mutation has been reported in a PGL patient who also presented with erythrocytosis [11]. So far, this mutation has not been confirmed, neither for other patients with PGL nor erythrocytosis.

Correlation of patient's presentation with their genetic background revealed a distinct manner of representation with respect to metastatic potential, catecholamine expression, tumor location [12] and ultra-structural appearance (unpublished observations) (Table 1). Patients with NF1, MEN and VHL related PGL rarely develop metastases (0–11 %) [6, 13, 14], while patients with SDHB germline mutation develop metastases in 50–97 % [6, 13-16] (table 1). The metastatic potential of PGL that developed due to germline mutation of *SDH5* and *TMEM127* is not yet clear, but suspected to be low.

Metastatic Paraganglioma: Does Location Play a Role?

PGL tissue from different locations appears similar microscopically. However, the prognosis is quite different for different tumor locations.

Patients with PHEO rarely develop metastases. Also, metastases secondary to HNP seem to be infrequent [17]. However, development of metastatic disease in patients with eaPGL and/or multiple PGL has been reported frequently [18]. Patients with *SDHB* derived PGL are more prone to developing metastatic disease. However, the primary tumor location most often found in patients with metastatic disease remains eaPGL [16, 19]. This may imply an effect of the tumor environment on the development of metastatic disease.

The majority of PGL related metastases occur in local and distant lymphatic nodes, bones, liver and lungs [20, 21]. Thus, PGL cells seem to spread via the lymphatic as well as the hematogenic route. Patients with long bone metastases have a more promising prognosis with up to 20 years of survival after detection of metastases, while patients with soft tissue metastases usually die much sooner (own unpublished observations). The cause for the unfavorable outcome of organ lesions remains to be established.

Metastatic Paraganglioma in Children

PGL in children is rare, thus studies including a representative cohort of pediatric patients are sparse and often contradictory. Available studies were recently reviewed by Havekes et al. [22].

Pediatric PGL appeared to be related to germline mutation frequently, even in the absence of family history (30 %[23], 39 % [24], 59 % [25], up to 80 % (own unpublished observations). Mutation of the *VHL* gene has been reported as predominant in pediatric patients [24, 26]. However, in a large group of children and adolescents with PGL (n=41), we observed a 54 % predominance for an *SDHB* mutation (own unpublished observations).

The primary PGLs in pediatric patients have been reported most frequently to be extra-adrenal (50 %), followed by PHEO (40 %) and HNP (10 %) [23]. These numbers mainly agree with our findings (54 %, 36 % and 1 %, respectively). As suggested by the high incidence of extra-adrenal primary tumors and *SDHB* mutation in children, the rate of the development of metastases seems to be higher than in adult patients (47% [23], 68% (own unpublished observations), 5 out of 7 patients [27]). In contrast, an Indian study including 11 pediatric patients almost always found the primary tumor to be PHEO [28]. No case of metastatic disease was reported for this cohort.

Positive family history or genetic testing, eaPGL, and a tumor diameter > 5cm have been shown to correlate with the development of metastatic disease in children [23].

Post surgical treatment with ^{131}I-MIBG seems to be beneficial in pediatric patients [27]. Thus, if detected early, the prognosis for pediatric patients with metastatic PGL may be more promising than for adult patients.

Insights into the Pathogenesis of Metastatic Paraganglioma

Cell culture experiments suggest that apoptosis resistance in absence of nerve growth factor (NGF) is common to several hereditary forms of PGL [29]. Thus, familial PGL may develop due to impaired culling of neural crest cells during the development of chromaffin tissues. NGF is an essential survival factor for developing neuroendocrine cells. Later in development, NGF becomes scarce, leading to neuronal culling. Survival of cultured cells,

with impaired *NF1*, *RET* or *VHL* gene expression, was connected to JunB mediated apoptosis resistance in absence of NGF. For SDHx dysfunction, apoptosis resistance was also shown, but here it seems to be caused further downstream in the same pathway. Accumulation of succinate, as appears in presence of *SDHx* mutations, inhibits prolyl hydroxylase (PHD) function. This can stabilize hypoxia inducible factor α (HIFα), promoting pseudo-hypoxic conditions [30, 31]. On the other hand, particularly inhibition of PHD3, also called EglN3, has been shown to hamper NGF related survival [29]. These results promote a common pathway for the development of PGL, but have not yet been proven in human tumor tissue.

Based on a gene expression profiling study, PGL of different genetic backgrounds could be separated into two groups. *VHL* and *SDHx* mutation derived tumors shared up-regulation of hypoxia-, angiogenesis- and oxidoreductase imbalance related genes. *MEN* and *NF1* derived tumors clustered separately [32, 33]. A more recent study confirmed this expression based clustering into different types of PGL [34].

Hypoxia is common to many tumors. However, it is not yet clear if a (pseudo-) hypoxic state with according up-regulation of angiogenesis and cell proliferation genes is sufficient for tumor development [35, 36]. In addition, while common to *SDHx* and some *VHL* related PGL, HIFα stabilization has not been found in von Hippel-Lindau 2C related PGL [37]. Thus, HIF stabilization alone, while potentially crucial to *SDHx* and some *VHL* related tumors, is not a common feature in all *SDHx* and *VHL* related PGL.

Interestingly, (pseudo-) hypoxia was shown to inhibit SDHB protein expression. Accordingly, SDHB protein is absent or low in a number of VHL derived tumors [38].

Although tumors derived based on mutation in the *VHL* and *SDHB* genes share pseudo-hypoxic features, tumor location, symptomatic manifestation, and metastatic potential are very distinct [15, 16, 39]. *SDHB* derived PGL typically present in a more aggressive manner with mainly extra-adrenal primary tumors, occurring at an earlier age with a high likelihood for the development of metastases. Thus *SDHB* mutations have been suggested as marker of poor prognosis [40].

It has been proposed, that the route of hypoxia development in *VHL* and *SDHx* derived tumors differs and thus results in up-regulation of distinct target genes [41]. It has been reported that in *SDHx* mutation derived tumors HIF1α expression is more often increased, while in *VHL* mutation derived PGL HIF2α stabilization seems to be predominant. However, Favier et al. reported that HIF2α is more highly expressed in *SDHx* and *VHL* derived tumors, while absent in *MEN* and *NF1* related tumors [34].

Another currently debated hypothesis to explain more aggressive behavior of *SDHx* related tumors are elevated levels of reactive oxygen species (ROS). In addition to succinate accumulation in *SDHB* and *D* mutation related PGL, complex II dysfunction has been observed [15, 42] and may lead to inappropriate electron transfer and increased ROS production. Mutation of the *SDHC* gene in model systems was shown to result in high levels of ROS, which lead to an increased frequency of mitochondrial and nuclear gene mutations, promoting tumor development and perhaps an aggressive phenotype [43, 44]. In a yeast model, mutation of the *SDHB*-equivalent lead to increased ROS production. However, no mutagenic DNA damage was detected [45]. However, *SDHB* silencing in cultured cells showed ambiguous results with respect to ROS production [46, 47]. It remains to be examined if ROS production differs between *VHL* and *SDHx* derived tumors, because the down-regulation of SDHB protein in *VHL* derived PGL [38] may also result in increased ROS production.

Dysfunction of complex II in *SDHx* as well as *VHL* derived tumors may promote aerobic glycolysis as the main source of energy ([34]; own unpublished data). Accordingly, lactic acidosis, which can be a result of decoupled glycolysis and oxidative phosphorylation, has been described in some patients with PHEO [48].

The development of metastatic disease on the molecular level remains to be elucidated for PGL. Suppressed expression of $p16^{INK4A}$ and $p14^{ARF}$ has been reported to promote the development of metastases in Pten knock–out mice [49]. In human PGL samples, promoter CpG methylation of the $p16^{INK4A}$ gene alone as well as promoter methylation of at least 3 of the following genes *RASSF1A*, *NORE1A*, $p16^{INK4A}$, *RARB*, *DCR2*, *CDH1* and *APC* (i.e. CpG island methylator phenotype (CIMP)) but not $p14^{ARF}$ has been shown to correlate with aggressive tumor behavior [50, 51]. However, the same patient population was used in both studies and out of 6 primary metastatic tumors evaluated, only 3 were positive for $p16^{INK4A}$ hypermethylation or CIMP. All reported samples that had tested positive for *SDHB* mutation showed $p16^{INK4A}$ hypermethylation and CIMP, including 1 primary benign tumor. Thus, hypermethylation seems to primarily correlate with *SDHB* mutation, which has been suggested previously as a predictor for metastatic potential [40]. Nevertheless, it may be of great interest to evaluate the molecular connection between *SDHB* mutation and a changed DNA methylation pattern. The consequences on the molecular biology of cells that carry these characteristic DNA methylations may help to explain why *SDHB* related PGL present in a more aggressive manner compared to other PGL.

Mutations of the *SDHB* gene as well as an extra-adrenal tumor environment seem to promote the development of metastases. However, a clear molecular biologic explanation for the more aggressive phenotype has not yet been found.

Markers for Malignant Paraganglioma

Currently there are no reliable markers for metastatic disease in PGL. The single way to diagnose malignancy is the presence of metastases. Thus, patients with PGL have to be followed-up on ultimately, because metastatic disease or recurrence can appear even after decades free of disease.

Many pathologic markers of malignancy used in other tumors were evaluated for PGL, but to date none could be sufficiently confirmed as a diagnostic or prognostic tool (for a summary see [2, 52–54]). Amongst them were tissue invasion, high vascularization, and staining for specific proteins (e.g. Ki67, hTERT [55]), characteristics that correlate with metastatic disease in other cancers. However, most of them proved to be not predictive of metastases or are controversial in PGL [54]. In a recent study that includes 11 tumors of patients that presented with PGL related metastases, Ki67 staining has been shown to have a sensitivity and specificity of 100 % [56]. However, this will have to be evaluated in a larger cohort of patients. In 2002 Thompson introduced the ‘pheochromocytoma of the adrenal gland scaled score’ (PASS), which is a scoring system based on 17 distinct morphologic features of PHEO to distinguish benign from primary metastatic tumors [57]. However, considerable inter- and intra-observer variation suggest that the PASS system is of limited diagnostic and predictive value [58].

Recently, absence of SDHB protein in PGL specimens was suggested as predictive of metastatic disease [59]. Absence of SDHB staining was found in some sporadic metastatic lesions in addition to others with known *SDHB* mutations. However, absence or low levels of SDHB protein were previously reported in *VHL* related PGL, which rarely metastasize [38]. Thus, the predictive value of metastatic disease based on low SDHB protein levels may be limited to a distinct group of PGL.

Stathmin has been shown to be a good predictive marker in endocrine tumors. In PGL tissue, staining for stathmin was more intense in primary metastatic tumors. However, its stand-alone value as a marker of malignancy is limited, because primary non-metastatic tumors also show stathmin expression. Differentiation between weak and more intense staining may be difficult when examining individual tumors [60].

The most promising diagnostic/predictive marker for metastatic PGL so far seems to be the expression of the HIF 2α regulated SNAIL alone [61], or in combination with its target twist [62]. Positive staining for one or both in primary tumors correlates well with the presence of distant metastases. However, these findings have to be carefully evaluated for the different types of PGL.

To date, *SDHB* mutation (particularly with a tumor size >5cm) and/or highly elevated levels of normetanephrine (NMN), dopamine (DA), L-3,4-dihydroxyphenylalanine (DOPA), and/or methoxytyramine are the best indicators for the development or presence of metastatic disease **(Eisenhofer 2005, JCEM, Timmers?!,** Eisenhofer et al. unpublished observation).

Diagnosis of Metastatic Paraganglioma

Signs and symptoms of patients bearing metastatic disease cannot be distinguished from those of patients with solitary or multiple PGL. In some cases, symptoms related to tumor burden of metastases are present. Most often patients with metastatic as well as non-metastatic PGL suffer from hypertension caused by the tumor's hypersecretion of catecholamines. As described below, the secretion profile of a tumor can present valuable clues about tumor location and the possibility of multiple lesions or metastases.

Presence of metastases can be ruled out by imaging studies. However, a possible later development of metastases has to be monitored continuously. Considerations about the imaging approach of choice should be based on the genetic background and biochemical phenotype of each patient, as described below.

Biochemical Phenotype of Metastatic Paraganglioma

Currently, the diagnostic gold standard for PGL is an elevated plasma and/or urine metanephrine level. When a PGL is present, catecholamine levels can also be elevated in plasma and urine, but due to their lower stability they show a lower sensitivity as a diagnostic tool than metanephrines [63]. For reliable results it is recommended to collect samples of relaxed patients. For plasma collection, patients should rest in the supine position without a pillow for at least 20 minutes after insertion of the cannula [64].

PGL can be differentiated based on their biochemistry in secreting (adrenergic, noradrenergic, or mixed phenotype) and non-secreting (biochemically silent) tumors. The latter most commonly arise from parasympathetic tissue in the head and neck area [65, 66]. Knowledge of the biochemical phenotype is an important diagnostic indicator for tumor localization and possible underlying mutation as well as the presence of metastases (summarized in table 1 and 2).

Metastases are most common in eaPGL, thus a noradrenergic phenotype (elevated norepinephrine (NE) or NMN) is often present in patients with metastatic disease. Metastases frequently appear dedifferentiated, potentially lacking the later enzymes of catecholamine synthesis. Thus, elevated methoxytyramine, DA, and/or DOPA levels can indicate metastatic disease (Eisenhofer et al. unpublished observations). Particularly in patients with SDHB mutation, eaPGL, and a primary tumor size of >5 cm metastatic disease is likely. Nevertheless, elevated DA, DOPA or methoxytyramine levels may also occur in

solitary HNP [65, 67]. A combination of elevated epinephrine (EPI)/metanephrine (MN) with NE/NMN may be caused by a solitary adrenal PHEO or multifocal adrenal and extra adrenal PGL or metastases. Metastatic disease in patients with an adrenergic phenotype is extremely rare.

Current Approaches to Detect Metastatic Paraganglioma

Following detection of elevated catecholamines and/or their metabolites or if PGL is otherwise suspected, confirmatory diagnosis and/or localization of PGL and possible metastases is necessary. Tumors can often be localized by computer tomography (CT) and/or magnetic resonance imaging (MRI). Non-specific functional imaging modalities, such as ^{18}F-FDG positrom emission tomography (PET) and octreotide scintigraphy are also applied. However, only functional imaging techniques using tracers that are specifically internalized by catecholamine metabolism related mechanisms may confirm a tumor as PGL (e.g. $^{123/131}$I-MIBG, ^{18}F-FDA, ^{18}F-FDOPA[1], ^{11}C-Epinephrine, ^{11}C-Hydroxyephedrine). Excellent in depth considerations which imaging modality is indicated under particular circumstances are presented elsewhere (e.g. [20, 69]). Here the focus will be on imaging of metastatic lesions in PGL.

Use of functional imaging compounds that target specific receptors generally expressed in PGL - namely the NE and somatostatin (ST) [70] transporters - can lead to false negative results in metastatic lesions. Expression of the NE [71, 72] as well as the ST transporter [73, 74] was shown to be reduced or absent in PGL related metastases. It is believed that cellular dedifferentiation in metastatic lesions is the cause for this. Decreased sensitivity and specificity of targeted functional imaging agents (i.e. the ‘flipflop’ phenomenon) is especially pronounced in PGL related to *SDHB* mutation. Thus, the preferred imaging modalities differ for *SDHB* and non-*SDHB* related metastatic disease 75, [76]. In *SDHB* related metastatic disease, ^{18}F-FDG PET is preferred. ^{18}F-FDG enters a cell through the glucose transporter (GLUT1). GLUT1 expression and ^{18}F-FDG uptake is elevated in highly metabolically active tissue, such as metastases with increased glycolytic energy production. Glycolytic activity appears to be increased in *SDHx* mutation related PGL, possibly due to mitochondrial dysfunction (own unpublished results). Despite its capability to reliably detect *SDHB* related metastases, an ^{18}F-FDG PET positive signal is not specific for PGL related lesions. When the genetic background is unknown and in non-*SDHB* related PGL, specific imaging of metastases should be attempted via ^{18}F-FDA or ^{18}F-FDOPA PET. Non-*SDHx* related bone metastases have been shown to be most reliably and specifically detected with ^{18}F-FDA, while *SDHB* related bone metastases could be more efficiently detected by non-specific scintigraphy and ^{18}F-FDG PET [77].

To date, the most widely used functional imaging modality for PGL is ^{123}I-MIBG imaging. While useful in evaluating a patient as potential candidate for treatment with ^{131}I-MIBG, sensitivity and specificity in the detection of metastases is inferior to ^{18}F-FDA and ^{18}F-FDOPA PET in patients with non-*SDHB* related disease and ^{18}F-FDG in patients with *SDHB* related PGL. Overall, ^{18}F-FDA PET remains the functional imaging approach of choice to detect PGL related metastases [20, 69, 78]. Functional PET images of a patient with apparently sporadic disease, presenting with extensive bone metastases 16 years after initial diagnosis of a right adrenal PHEO are shown in Fig.1.

Management and Treatment of Malignant Paraganglioma

Once presence of metastases is verified, there is no reliable cure. Treatment options are: 1) mechanical removal by excision or ablation, 2) targeted pharmaceutics or 3) chemotherapy. Recently, current treatment options were excellently summarized [79–81].

Surgical Approaches

Treatment options include palliative tumor resection, to reduce tumor burden and excess catecholamine related symptoms. Although in benign cases, a laparoscopic approach is preferred, in metastatic PGL this is controversial. Laparoscopy is not advisable when local invasion and/or large tumors are present or organ resection is required [82].

In patients with painful bone metastases and inoperable hepatic lesions, radiofrequency ablation (RFA) and cryoablation may be of benefit. However, before any tumor manipulation, patients have to be medicated with α– and β–blockers and catecholamine synthesis inhibitors for 7–21 days, to prevent hypertensive crisis during tumor manipulation (phenoxybenzamine, atenolol and metyrosine, respectively) [83]. Following pretreatment, RFA has shown to be manageable in patients with secreting PGL [84]. More recently, complete ablation of 6 out of 7 metastatic lesions (4 hepatic, 3 bone and 1 ischiatic) in 6 patients suffering from PGL has been presented [85].

Successful cryoablation on a hepatic lesion of a patient with non-secreting metastatic PGL has been reported [86].

Chemotherapy

The most widely used chemotherapeutic regimen is the CVD regimen (cyclophosphamide 750 mg/m^2 body surface on day 1, vincristine 1.4 mg/m^2 body surface on day 1, and dacarbazine 600 mg/m^2 body surface on day 1 and 2, repeated every 21 days), developed by Keiser et al. 1985 [87]. However, benefits of CVD therapy for metastatic pheochromocytoma appears to be short-term and do not include an increase in patient survival. Particularly in women and patients with primary PHEO, CVD is counter-indicated [88]. However, in a patient with *SDHB* mutation related disease, great results were achieved under the CVD regimen [89]. Thus, CVD therapy may be considered in patients with fast growing tumors due to *SDHB* mutation, in patients where tumor shrinkage prior to resection is required or in patients whose symptoms related to catecholamine excess cannot be managed otherwise [90].

A recent case study has reported on a patient with metastatic PGL who has been orally treated with temozolomide. The patient received 250 mg temozolomide daily for 5 days, repeated every 28 days. After 21 weeks of treatment, the patient was free of symptoms, with a significant decrease of plasma catecholamine and metanephrine levels. The primary tumor and liver metastases shrank and allowed tumor resection. The authors conclude that treatment of metastatic PGL with temozolomide may be of benefit prior to tumor resection [91].

Temozolomide has also been used in combination with the targeted drug thalidomide for the treatment of metastatic PGL. In a phase II study including 3 patients with metastatic PGL, patients have been treated with 150 mg/m^2 temozolomide for 7 days every other week and 50–400 mg/m^2 daily. One out of 3 patients showed a positive response to the regimen, however cytotoxic effect that caused subjects to end this treatment regimen were observed in patients with other endocrine malignancies [92].

Targeted Therapy

In addition to tumor removal, treatment with targeted radiotherapeutics can be beneficial. The most frequently used radiotherapy is treatment with ^{131}I-MIBG. This treatment option was developed as early as 1984 [93]. Feasibility of this treatment for each patient needs to be verified by positive $^{123/131}$I-MIBG imaging. Regimens of high or low doses were performed (>600 mCi and 100–500 mCi, respectively). Symptomatic response has been reported in as much as 67–98 % of patients, while objective tumor shrinkage/stable disease or decreased

secretion was observed in 27–47 % and 45–67 % of the patients, respectively [94–97]. Comparable results with a lower rate of adverse reactions could be achieved in a low dose regimen; hormonal and symptomatic relive for 50 % of patients have been reported [98].

In an attempt to increase the curative effect of ^{131}I-MIBG treatment, recently Ultratrace Iobenguane I-131 has been developed. It is a high-specific activity ^{131}I-MIBG and was shown to result in a lower frequency of adverse effects than regular ^{131}I-MIBG [99]. Treatment effects with drastically fewer unlabelled molecules may be a promising improvement for ^{131}I-MIBG therapy. However, its efficacy remains to be evaluated.

Besides radiotherapy, targeting the NET system with ST analogs has been used in the treatment of metastatic PGL (^{90}Y-DOTATOC). Success rate for radiolabelled octreotide analogues is not entirely clear yet, because only a few patients were treated by this means.

Treatment with unlabelled octreotide has also been done. However, it seems to be ineffective with respect to blood pressure, catecholamine- and Chromogranin A release [100]. An explanation for the lack of effect may be the relatively low expression of the target of octreotide, the ST2a receptor. While the ST2a receptor was found in only 25 % of PGL samples, the ST3 receptor was found in more than 60 % of cells in 90 % of 52 PGL samples examined [101]. Thus, targeting the ST3 receptor may prove a more beneficial approach in the treatment of metastatic PGL.

Treatment of metastatic PGL with the mTOR inhibitor everolimus was attempted with no significant benefit, and thus is not recommended [102, 103].

The most promising approach to date seems to be treatment with multiple tyrosine kinase inhibitors like sutinib. Reports on 5 patients with metastatic PGL treated with sutinib are currently available. All 5 patients showed at least a partial response [104–106]. A phase II trial is currently being organized. Despite the promising results with sutinib, the tyrosine kinase inhibitor imatinib did not prove to be useful in two patients with metastatic PHEO [107].

A recent study showed that the interleukin 13 (IL-13) receptor α2 is expressed on the tumor cell's surface in humans and in a mouse model. Treatment of PGL bearing mice with IL-13 coupled to a truncated *Pseudomonas* exotoxin lead to a significant decrease in tumor size [108]. The compound has been successfully tested in several clinical trials [109]. Targeting the IL-13 receptor may be a promising new strategy to treat metastatic and inoperable PGL.

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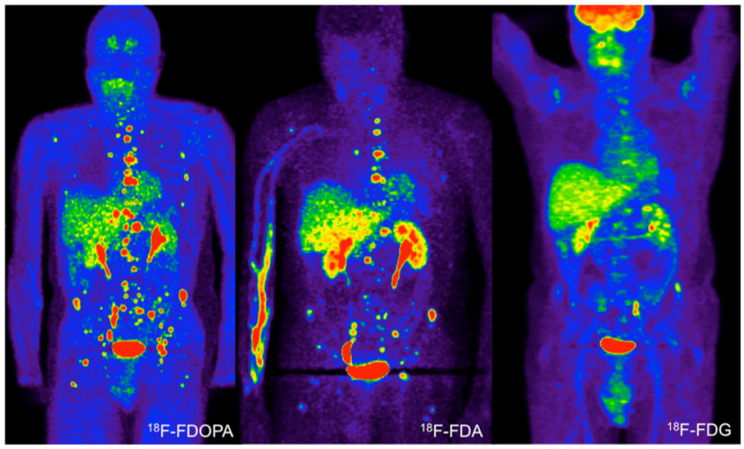


Fig.1.

Anterior reprojected functional PET images of a patient with extensive bone metastases, detected 16 years after diagnosis of a right adrenal pheochromocytoma. The scans were performed on three consecutive days. Genetic testing for SDHB, C, and D germline mutations or deletion were negative.

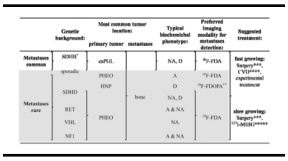
Table 1

Predisposition to malignancy with respect to hereditary background.

Genetic background	Predisposition to malignancy (%)
NF1	0.7–11[2–4]
RET	0–3[2–4]
VHL	3–8[2–4]
SDHB	50–97 [2–6]
SDHD	0–3[2–4, 98, 99]

Table 2

Presentation, imaging and suggested treatment in PGL by hereditary backgrounds.



Genetic background:		Most common tumor location: primary tumor	metastases	Typical biochemical phenotype:	Preferred Imaging modality for metastases detection	Suggested treatment:
Metastases common	SDHB*	eaPGL		NA, D	^{18}F-FDA	fast growing: Surgery***, CVP****, experimental treatment
Metastases rare	sporadic	PHEO	bone	A	^{18}F-FDA	
	SDHD	HNP		D	^{18}F-FDOPA**	
	RET			NA, D		slow growing: Surgery***, ^{131}I-MIBG*****
	VHL	PHEO		A & NA	^{18}F-FDA	
	NF1			NA		
				A & NA		

Abbreviations: adrenergic (A) (elevated epinephrine (Epi) and/or metanephrine (MN)); noradrenergic (NA) (elevated norepinephrine (NE) and/or normetanephrine (NMN)); dopaminerg (D) (elevated dopamine (DA); L-3,4-dihydroxyphenylalanine (DOPA) and/or methoxytyramine); adrenal PGL (PHEO); extra-adrenal PGL (eaPGL); head and neck PGL (HNP).

* Risk of metastatic disease particularly high in children and adolescents.

** Mainly studied on primary HNP but potentially similarly effective for metastases.

*** Complete resection of metastases is rarely possible, but resection can have a good palliative effect (avoidance of further organ or bone destruction by tumor growth as well as reduction of catecholamine levels which leads to a decrease in related signs and symptoms).

**** own unpublished observations suggest that (at least) patients with *SDHB* related fast growing tumors initially respond well. Physicians are recommended not to stop CVD, because resumption of therapy almost always results in chemotherapy resistant tumors (if toxicity occurs, longer intervals between cycles or a reduced dosage can be used).

***** High doses may be effective [111], however, additional studies and long-term observations are needed.