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REVIEW ARTICLE

Malignant pheochromocytomas and paragangliomas: a diagnostic challenge

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Abstract
Introduction Malignant pheochromocytomas (PCCs) and paragangliomas (PGLs) are rare disorders arising from the adrenal gland, from the glomera along parasympathetic nerves or from paraganglia along the sympathetic trunk. According to the WHO classification, malignancy of PCCs and PGLs is defined by the presence of metastases at non-chromaffin sites distant from that of the primary tumor and not by local invasion. The overall prognosis of metastasized PCCs/PGLs is poor. Surgery offers currently the only change of cure. Preferably, the discrimination between malignant and benign PCCs/PGLs should be made preoperatively.

Methods This review summarizes our current knowledge on how benign and malignant tumors can be distinguished.
Conclusion Due to the rarity of malignant PCCs/PGLs and the obvious difficulties in distinguishing benign and malignant PCCs/PGLs, any patient with a PCC/PGL should be treated in a specialized center where a multidisciplinary setting with specialized teams consisting of radiologists, endocrinologist, oncologists, pathologists and surgeons is available. This would also facilitate future studies to address the existing diagnostic and/or therapeutic obstacles.

Keywords Pheochromocytoma · Paraganglioma · Malignancy · Diagnosis · Therapy

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Introduction

The term pheochromocytoma (PCC) refers to the color of the tumors cells when stained with chromium salts. PCCs and paragangliomas (PGLs) are tumors arising from chromaffin cells that synthesize, store, metabolize and, usually but not always, secrete catecholamines [1, 2]. According to the 2004 WHO classification, adrenal chromaffin tumors are classified as PCCs, whereas extra-adrenal tumors (such as the neck, mediastinum, abdomen, pelvis and organ of Zuckerkandl) arising from the glomera along parasympathetic nerves or paraganglia along the sympathetic trunk are termed PGLs [3]. Sympathetic PGLs are typically secretory and have formerly often been termed extra-adrenal PCCs. Tumors arising in the head and neck originate almost exclusively from the parasympathetic nervous system, and approximately 95% of such tumors are non-secretory [1, 2]. Head and neck PGLs (carotid body PGLs, vagal PGLs and jugulotympanic PGLs) are not discussed in this review.

Incidence and prevalence

The epidemiology of PCCs/PGLs is not precisely known. The incidence of these tumors appears to be approximately one in 300,000/year [2]. In western countries, the estimated prevalence is between 1:6,500 and 1:2,500 [4]. The annual age-adjusted prevalence of malignant PCCs in the USA is between 0.3 and 0.7 cases per 1 million, and the incidence of malignant PCCs was 93 cases per 400 million persons in 2002 [1]. Thus, malignant PCCs are exceedingly rare.

The peak age of occurrence is in the fourth to fifth decade of life, with almost equal distribution among male and female patients, except for familial tumors occurring at an earlier age [4, 5]. A tendency towards malignancy has been reported in females by some [6].

Malignancy

According to the WHO classification, malignancy of PCCs and PGLs is defined by the presence of metastases at non-chromaffin sites distant from that of the primary tumor and not by local invasion [3]. To avoid confusion with multifocal disease, metastases must occur in sites where paraganglia are not normally present such as lung, bone or liver. Some authors assign PCCs with a frank locoregional invasion, i.e. invasion into contiguous organs, to the group of malignant PCCs [1, 5]. However, locally invasive tumors, formerly often considered indicating malignancy, may follow an indolent course [7–9]. It is obvious that the definition of malignancy varies in many studies. Due to these different classifications, studies looking for pre-, intra- or postoperative signs or markers predicting malignancy can only be as (in)sufficient as our varying classifications. Furthermore, no reliable method (histology or genetic, molecular, immunohistochemical, imaging markers) is currently available to distinguish benign from malignant lesions, and malignancy is only established beyond doubt by the presence of distant metastases (e.g. bones, liver, lungs and kidney) [10]. That means that a completely removed malignant but not metastasized PCC will not be identified as malignant nowadays. Therefore, the true rate of malignant PCC cannot be defined as tumor-associated criteria are not available. Despite these limitations, the overall rate of malignant PCCs is traditionally cited to be roughly 10% [3, 11], with a wide range between 2.4% and 50% depending on the definition of malignancy and patient's selection [4, 5, 12–15]. Up to 5–20% of sympathetic PGLs are considered as being malignant [14, 16, 17]. The use of different definitions for malignant PCCs and malignant PGLs accounts for the large discrepancies in their reported prevalence [18–20]. Concerning children and adolescents, a malignancy rate of roughly 10% has been reported [21–23].

Of note, propensity to malignancy is dependent on the genetic background of the tumors. In sporadic tumors, about 6–10% are malignant, and the likelihood of malignancy is even lower in patients with *RET*, *VHL* and *SDHD* gene mutations [24, 25]. However, probably up to 40% of patients with *SDHB* mutation will develop distant metastases [10].

Prognosis

The overall prognosis of metastasized catecholamine-producing tumors is poor. Five-year survival rates vary from 20% to 50% [1], with a significant heterogeneity among patients [11]. The majority of patients will succumb their disease [26], but long-term survival has been reported [27]. Survival of patients with metastatic lesions in liver and lungs tends to be shorter (<5 years) than survival of patients with bone metastases only [28]. Malignant disease is evident preoperatively in nearly 50% of patients. Metastatic disease, however, may only become evident after the primary tumor is surgically removed. Recurrence or metastases usually present within 2–5 years but may be diagnosed even after several decades in some patients [1, 14, 29–31].

Familial syndromes

Roughly 10 years ago, mainly three genes (*NF1*, *VHL* and *RET*) were associated with the occurrence of inherited PCCs, and about 10% of PCCs were considered familial. The corresponding syndromes are neurofibromatosis type 1 (NF1), von Hippel–Lindau type 2 (VHL2) and multiple

endocrine neoplasia type 2 (MEN2), respectively. In addition, various hereditary paraganglioma syndromes (PGL1-4) could be distinguished clinically and by linkage analysis, but no genes were reported. This changed in 2000, when germline mutations in the gene coding for the succinate dehydrogenase complex subunit D (S*DHD*) were reported for the first time in PGLs [32] and PCCs [33]. Since then, germline mutations have also been reported in other genes coding for subunits of the succinate dehydrogenase complex: *SDHC* [34], *SDHB* [35], *SDHAF2/SDH5* [36] and *SDHA* [37]. The associated syndromes are now summarized as pheochromocytoma–paraganglioma syndromes [38]. In addition, germline mutations have recently been reported in *KIF1Bbeta* [39], *TMEM127* [40] and *MAX* [41], but no syndromes have been reported yet. In addition, Carney triad [42] and Carney–Stratakis dyad are associated with PGLs [43]. While mutations in *SDHB*, *SDHC* and *SDHD* can lead to Carney–Stratakis dyad, no gene has been identified in Carney triad yet.

In summary, at least ten genes have been found to carry germline mutations in familial tumors, and about 25–30% of PCCs are currently considered being familial [17, 44]. From the clinical point of view, however, the knowledge of PCCs/PGLs being inherited does not make it easier to distinguish between malignant and benign tumors. Malignancy should always be expected in *SDHB*-associated tumors, and a more stringent follow-up is probably indicated in these patients.

Genotype–phenotype correlations in familial syndromes

Von Hippel–Lindau syndrome (*VHL* mutation) is an autosomal dominant disorder. Prevalence is approximately 1:36,000 live births. The frequency of PCCs in individuals with VHL is 10–30% overall. Approximately 50% of PCCs are bilateral. About 5% of VHL-related catecholamine-secreting tumors become malignant, most commonly extra-adrenal sympathetic PGLs [2].

Multiple endocrine neoplasia type 2 is an autosomal dominant syndrome caused by mutation of the *RET* protooncogene. Prevalence is estimated at 1:30,000. Approximately 50% of individuals with MEN2A and MEN2B develop PCCs. PCCs are bilateral in 50–80% of cases but are almost always benign [2].

Neurofibromatosis type 1 is an autosomal dominant disorder caused by mutation of *NF1*. Prevalence is estimated at 1:3,000 to 1:4,000. Although PCCs are rare in NF1, their frequency is as high as 20–50% in individuals with NF1 and hypertension. Most (84%) PCCs are unilateral. Extra-adrenal sympathetic PGLs can occur. These tumors may be malignant in about 10% [2].

Hereditary pheochromocytoma–paraganglioma syndromes are inherited in an autosomal dominant manner. *SDHD* (PGL1), *SDHC* (PGL3) and *SDHB* (PGL4) are the three nuclear genes responsible for the hereditary pheochromocytoma–paraganglioma syndromes. A fourth nuclear gene, *SDHAF2* (PGL2), also known as *SDH5*, has been recently reported [2]. Mutations in *SDHD* (PGL1) demonstrate parent-of-origin effects and generally cause disease only when the mutation is inherited from the father. However, an individual who inherits an *SDHD* mutation from his/her mother has a low but not negligible risk of developing disease. Initial data suggest that mutations in *SDHAF2* (PGL2) exhibit parent-of-origin effects similar to those of mutations in *SDHD* [2]. The pheochromocytoma–paraganglioma syndrome should be considered in all individuals with PCCs and/or PGLs, particularly those with the following findings: multiple tumors including bilateral tumors, multifocal with multiple synchronous or metachronous tumors, recurrent tumors, early onset (i.e. age <40 years) tumors and family history of PCCs or PGLs [2]. Most recently, a mutation in *SDHA* has been found in a patient with PGL [37]. Of interest is the clinical behavior of malignant PCCs and PGLs that appears to be most aggressive in patients with germline *SDHB* mutation as opposed to patients having sporadic malignant PCCs and PGLs [45].

Although heterogeneous, the following correlations between the gene involved and tumor characteristics can be used to guide management: Germline mutations in *SDHB* are strongly associated with extra-adrenal sympathetic PGLs [13]. Chromaffin tumors in persons with germline *SDHB* mutations are sixfold more likely to be extra-adrenal than chromaffin tumors in general. A possible relationship between *SDHB* exon 1 deletions and abdominal extra-adrenal PGLs has recently been proposed [2]. PGLs in persons with a germline *SDHB* mutation are more likely to become malignant than sporadic PGLs or those that develop in persons with germline *SDHD* and *SDHC* mutations. *SDHB* mutations may also predict a shorter survival in persons with malignant PCCs and PGLs. Up to 50% of persons with malignant extra-adrenal PGLs have a germline *SDHB* mutation. Because extra-adrenal sympathetic PGLs have long been known to have a greater predisposition to malignancy than PCCs and head and neck PGLs, it is not clear whether this effect is the result of location, mutation status or both [2, 12]. Although less common than malignant extra-adrenal sympathetic PGLs, malignant PCCs do occur and may be more common in individuals with a germline *SDHB* mutation than in those with a germline *SDHD* or *SDHC* mutation or with sporadic PCCs [2]. However, persons with a germline *SDHD* mutation can develop malignant disease at any paraganglion site [2]. Mutations in *SDHD* and *SDHC* are more frequently associated with parasympathetic head and neck PGLs than

other tumor types. However, thoracic and abdominal localizations remain possible [2].

Carney triad is an extremely rare disorder that primarily affects young women. As initially described, the classic Carney triad included extra-adrenal sympathetic PGLs, gastric stromal sarcoma and pulmonary chondroma. PCCs were later shown to be associated with the syndrome (with adrenal cortical adenoma and esophageal leiomyoma). Carney triad may be familial, but a causative gene has yet to be identified [2, 42].

Carney–Stratakis dyad, also termed Carney–Stratakis syndrome, is the association of PGLs and GISTs and is distinct from the Carney triad [43]. PGLs and GISTs in these families appear to be inherited in an autosomal dominant manner with incomplete penetrance. PGLs occur in the head and neck, thorax and abdomen. *SDH*x mutations have been reported in individuals from six unrelated families with the Carney–Stratakis dyad, and the significance of these findings is not yet clear [2].

More recently, further genes have been shown to be associated with hereditary PCCs and PGLs: *KIF1Bβ* [39, 46], *TMEM127* [40, 47, 48] and *MAX* [41]. Concerning these genes, no specific syndrome has been reported yet. While the risk of developing bilateral PCCs appears to be high, the risk of developing PGLs is considered to be low. If the currently available data are correct, patients with *MAX* germline mutations have a risk of about 25% of developing malignant PCCs [41].

Preoperative diagnosis

PCCs and extra-adrenal sympathetic PGLs mainly come to medical attention in four clinical settings: signs and symptoms associated with catecholamine hypersecretion, incidentally discovered mass on CT/MRT performed for other reasons, signs and symptoms related to mass effects from the neoplasm and screening at-risk relatives [2]. Preferably, the discrimination between malignant and benign PCCs/PGLs should be made preoperatively.

Clinical diagnosis

Most patients with PCCs have hypertension, often associated with palpitations, headache and diaphoresis ("typical signs"). Functioning malignant chromaffin cell tumors have a clinical presentation similar to benign tumors, but patients may present with variable symptoms and signs, such as dyspnea, nausea, weakness, weight loss, visual disturbance, arrhythmias and mental problems [11, 49]. A lack of the "typical signs" may also raise the suspicion that one is dealing with a malignant case [50, 51]. Symptoms suggestive for malignancy may arise from metastases that often are found in the skeletal system where they may cause bone pain and nerve compression [6]. Patients with persistent symptoms following surgery for alleged benign disease are highly suspicious for the presence of small metastases as part of malignant disease.

In the case of large cystic PCCs, many patients present without hypertension [52]. Patients with malignant PCCs may even lack clinical signs until the late stage [53].

Biochemical diagnosis

The diagnosis of PCCs and sympathetic PGLs is based on biochemical testing and imaging studies.

Unspecific biomarkers

Neuroendocrine cells as neurons contain vesicles that produce and secrete chromogranins and secretogranins. Both belong to a group of acidic, soluble proteins. A markedly increased preoperative chromogranin A plasma level in patients with malignant PCCs (n=14,2,932± 960 ng/mL) in comparison to patients with benign pheochromcytomas (n=13, 188±40.5 ng/mL) has been reported [54]. A chromogranin A level higher than 500–600 ng/mL was highly suggestive for a malignant PCC. In accordance, chromogranin A has been used to monitor patients during chemotherapy of malignant PCCs [55]. Some investigators have reported a high serum concentration of neuron-specific enolase (NSE) [56].

Hormones

Catecholamines hypersecreted by PCCs and PGLs can be any of the following: epinephrine (adrenaline), norepinephrine (noradrenaline) and dopamine. Concerning the biochemical diagnosis of PCCs, it is recommended to measure plasma or 24-h urinary excretion of fractionated metanephrines [1, 2, 4, 5]. The latter is preferred as it is more sensitive than the measurement of catecholamine concentrations [57, 58].

Concerning malignant PCCs, the same recommendations exist. Rarely, non-functioning benign and malignant PCCs are reported [59–61]. Malignant PCCs, however, may lack various enzymes. One of them, PNMT, converts norepinephrine (noradrenaline) to epinephrine (adrenaline). Lack of PNMT thus leads to dominating production of norepinephrine in malignant PCCs, and high levels of norepinephrine have even been reported to be associated with a shorter metastases-free interval [62]. False positive results may be reduced by follow-up testing for plasma chromogranin A and/or urine fractionated metanephrine levels when plasma fractionated metanephrine concentrations are less than fourfold above the reference range [11, 63].

It has also been reported that high dopamine levels, representing more premature catecholamine secretion due to decreased expression of dopamine-β-hydroxylase, are more common in malignant PCCs [64]. PCCs expressing solely dopamine but not epinephrine/norepinephrine appear to have a very high likelihood of being malignant [65], and higher levels of dopamine are associated with a shorter metastases-free interval [65]. Consequently, patients with high preoperative 24-h urinary dopamine levels (>5,000–6,000 nmol/24 h) have an increased likelihood of having malignant PCC [66]. Of note, a low ratio of plasma epinephrine to total catecholamines was reported to predict recurrence [67]. The secretion of norepinephrine with little or no epinephrine suggests an extra-adrenal PGL or a PCC associated with von Hippel–Lindau syndrome [28].

Patients with persistently elevated catecholamine levels following surgery for alleged benign disease are highly suspicious for the presence of small metastases as part of malignant disease.

Imaging

PCCs can be detected using a variety of imaging techniques, but due to their inconsistent fashion, they may mimic various tumors, both benign and malignant, including metastases [68]. Distant metastases of PCCs are most often found in bone (50%), liver (50%) and lung (30%) [49].

Diagnostic techniques include conventional radiological imaging with computed tomography (CT), magnetic resonance imaging (MRI), ultrasonography (US), contrast-enhanced US (CEUS), endoscopic US (EUS) and intraoperative US (IOUS); selective angiography with hormonal sampling; and nuclear medicine imaging by 111In-octreotide (OctreoScan), 123I-metaiodobenzylguanidine (MIBG), 99mTc-EDDA/HYNIC-Tyr3-octreotide scintigraphy or, more recently, somatostatin receptor PET with 68Ga-octreotide, [18F]DOPA, [18F]Dopamine and [11C]5-hydroxytryptophan. No technique is the gold standard, and specific sequences of exams might be needed for each tumor type. A combination of two or more imaging techniques is often required for diagnosis and staging. Usually, radiological techniques (such as ultrasound, CT or MRI) are useful in the localization of the primary tumor, particularly if non-functioning, while nuclear medicine aids in the evaluation of the extent of disease, staging and therapy decision making [69–71].

Computed tomography

CT has a very high sensitivity in detecting PCCs but a relatively low specificity [57, 72–74]. PCCs may mimic both adenomas and malignant masses on both CT densitometry and washout [68].

CT densitometry has been shown as being helpful in distinguishing between benign and malignant adrenal lesions. A density of approximately 40–50 HU after injection of contrast medium is suggestive for a PCC. Inhomogeneous appearance is not uncommon and may be due to hemorrhage or necrosis. A homogeneous adrenal mass with a density of less than 10 Hounsfield units (HU) on an unenhanced CT is almost certainly a benign adrenal lesion [57]. Therefore, lesions with an unenhanced density greater than 10 HU requires further evaluation. The attenuation of PCCs on an unenhanced CT scan is significantly higher than the attenuation of adrenal cortical adenomas (44±11 Hounsfield units versus 8±18 HU). However, adrenocortical carcinomas (39±14 HU) are difficult to differentiate from PCCs based on CT findings alone without biochemical testing [1]. On contrast enhancement, the tumors are usually irregular with peripheral enhancement.

It was found that adrenocortical adenomas enhance rapidly after administration of contrast medium and also show rapid loss of contrast medium, a phenomenon called contrast washout. If the "washout" after 15 min is higher than 60%, the sensitivity is 86–88%, and the specificity is 92–96% for the lesion being an adenoma [75]. Others have proposed a "washout" greater than 50% after 10 min [76]. The washout of malignant lesions is used to be less than 40% [68].

If malignancy is suspected, an initial abdominal CT scan from the neck to the pelvis floor should be performed, and contiguous thin sections with 1.5- to 3-mm cuts must be obtained. CT scan reliably localizes most PCCs >1 cm, with accuracy approaching 100% [1, 11]. Because 90% of all sympathetic tumors are located within the adrenal gland and 98% "abdominal", a high-quality CT scan will likely identify most tumors and image the normal contralateral gland [1]. PCCs have a wide range of imaging characteristics on CT, from a well-circumscribed homogeneous mass to a heterogeneous, cystic or hemorrhagic mass. Despite these features, diagnosis of malignancy is unreliable unless distant metastases are apparent [1].

Magnetic resonance imaging

MRI sensitivity is similar to CT but is less available [72–74, 77]. It is, however, the preferred initial imaging procedure for PCCs in children, pregnant women and patients allergic to contrast medium [57]. Since PCCs are hypervascular, they characteristically have intermediate to high signal intensity on T2-weighted sequences ("light bulb" sign) [77]. However, this holds only true for about 70% of PCCs, and high signal intensities can also be found in other conditions such as hemorrhage, hematoma, etc. MRI is highly specific for PCCs if the T2-weighted image brightness is three times greater than the liver [11]. The

hyperintensity on T2-weighted images makes MRI more accurate and sensitive than CT scanning for recurrent, metastatic and extra-adrenal PGLs [1].

Chemical shift MRI relies on the different resonance frequencies of protons in fat and water molecules. Electrons surrounding the proton shield it from the applied external field. The effective magnetic field experienced by a shielded proton is less than the effective magnetic field experienced by an unshielded proton. Fat protons are more shielded than water protons and thus resonate at a lower frequency. It is the difference in resonance that is used in chemical shift imaging. Two T1-weighted acquisitions are performed: out-of-phase and in-phase acquisitions. In adrenal tumors that do not contain fat (e.g. metastases), there is no significant signal loss. Applying these techniques, the sensitivity and specificity to differentiate adenomas from metastases range from 81–100% and 94–100%, respectively [78].

Diffusion-weighted MRI (DWI) with high *b*-value has been successfully used to detect metastases from malignant PCCs and PGLs and may be superior to 123I-MIBG and even FDG-PET [79]. In particular, this technique may be advantageous in detecting lymph node and liver metastases but less sensitive in mediastinal and lung metastases.

Endosonography

Endosonography has been used successfully in localizing PCCs [80]. Hyperechoic echogeneity and echostructure was only seen in benign tumors, but no specific appearance could be found for malignant PCCs. The experience, however, is limited.

MIBG scintigraphy

Metaiodobenzylguanidine or iobenguane is the combination of the benzyl group of bretylium and the guanidine group of guanethidine. This aralkylguanidine norepinephrine analog is an adrenergic neuron blocker and the so-called false neurotransmitter [81].

Since MIBG structurally resembles noradrenaline, it enters in neuroendocrine cells by either the neuronal uptake-1 mechanism or by passive diffusion. The transfer of MIBG from the intracellular cytoplasm into catecholamine storage vesicles (neurosecretory granules or vesicles) is mediated by an ATPase-dependent proton pump. Unlike neuradrenaline, MIBG is not metabolized and is excreted unchanged. Since MIBG storage in neurosecretory granules enables a specific concentration in neuroendocrine cells in contrast to cells of other tissues, uptake of MIBG by the various organ systems reflects either rich adrenergic innervation or catecholamine excretion (or both) [82, 83].

MIBG radiolabeled with 131- or 123-iodine was developed in the early 1980s to visualize tumors of neuroendocrine origin, particularly those of the neuroectodermal (sympatho-adrenal) system (PCCs, PGLs and neuroblastomas), although other neuroendocrine neoplasms (e.g. carcinoids, medullary thyroid carcinoma, etc.) are also visualized (Table 1) [82–85].

Theoretical considerations and clinical experience indicate that the 123I-labeled agent is to be considered as the radiopharmaceutical of choice, at least in children, as it has a more favorable dosimetry and provides better image quality. Gamma emission energy of 159 KeV for 123I is more suitable for imaging (especially in tomographic

Table 1 Clinical indications to perform MIBG

Oncological indications
1. Detection, localization, staging and follow-up of neuroendocrine neoplasms and their metastases, in particular:
–Pheochromocytomas
–Neuroblastomas
–Ganglioneuroblastomas
–Ganglioneuromas
–Paragangliomas
–Carcinoid tumors
–Medullary thyroid carcinomas
–Merkel cell tumors
2. Study of the tumor uptake in order to decide and plan possible treatment with high activities of radiolabeled MIBG. In this case, the dosimetric evaluation should be individual and not based on the ICRP tables, which have only an indicative value limited to diagnostic procedures
3. Evaluation of tumor response to therapy by measuring the intensity of MIBG uptake and the number of focal MIBG uptake sites
4. Confirmation of suspected neoplasms derived from neuroendocrine tissue
Other (non-oncological) indications
1. Functional studies of the adrenal medulla (hyperplasia), sympathetic innervation of the myocardium, salivary glands and lungs

modality) than 360 KeV for 131I, and the difference in terms of radiation burden permits us to inject higher activities of 123I-MIBG. Furthermore, results with 123I-MIBG are more rapidly available. Nonetheless, 131I-MIBG is still widely employed because of its lower costs, ready availability and longer half-life and the possibility of obtaining delayed scans. Furthermore, 131I-MIBG may be preferred when estimation of the tumor's retention is required for MIBG therapy planning [86, 87]. Indeed, the high tumor affinity of MIBG for the detection of primary and secondary tumor sites have led to the use of the compound labeled with γ/β emitter 131-iodine (131I-MIBG) as radiotherapeutic agents in neuro-ectodermally derived tumors [88].

The sensitivity and specificity of MIBG for the diagnosis of the primary tumor have been estimated to be 73% and 94%, respectively. Since there is no physiological uptake of MIBG in bone and bone marrow, the sensitivity and specificity of MIBG for detecting osteomedullary metastases are even higher (90% and 100%, respectively) [86]. A recent meta-analysis based upon the literature results reports a sensitivity of 97% [95% confidence interval (CI), 95% to 99%] for detection of neuroblastoma, while data were insufficient to estimate specificity. For PCCs, sensitivity and specificity were 94% (95% CI, 91–97%) and 92% (95% CI, 87–98%), respectively [89].

In malignant tumors, however, the expression of noradrenaline transporters decreases, and thus, the sensitivity is lower [74, 90], and it is not uncommon that both MIBG-positive and MIBG-negative lesions coexist. Also, VHL-associated PCCs are more likely to be missed, most likely due the lower expression of the norepinephrine transporter [91]. For these reasons, one unequivocal MIBG-positive lesion at a distant site is sufficient to define a metastatic disease. A single equivocal lesion on MIBG requires confirmation by another imaging modality. In particular, extra-adrenal and small adrenal PCCs are more likely to result in false negatives on MIBG. Furthermore, adrenal PCCs containing minimal solid tissue due to extensive necrosis may predict a negative MIBG result [92–95].

Single photon emission computed tomography (MIBG-SPECT) allows for better depiction of small focal uptake that is difficult to visualize on planar MIBG, especially in areas close to intense physiological uptake such as the liver and the bladder. The particular strengths of MIBG SPECT/CT are detection of local recurrence, small extra-adrenal PCCs, multifocal tumors or the presence of metastatic disease (Fig. 1) [96–101].

It is important to notice that 123I-MIBG has even been used, combined with intraoperative gamma probe, to identify malignant foci [102].

Currently, radio-iodinated MIBG is prepared by an exchange radio-iodination method and, thus, is of low specific activity. For possible better targeting and to ward off pharmacological effects, especially in therapeutic purposes, its preparation at a no-carrier-added level both by solution-phase and solid-phase syntheses has been developed [103].

Somatostatin analogs

For over two decades, somatostatin receptor scintigraphy (SRS) with indium-111 DTPA D Phe octreotide (Octreoscan®) has been widely used as a diagnostic agent, particularly to image neuroendocrine neoplasms [104]. Octreotide scintigraphy can be used in addition to MIBG scintigraphy as some MIBG-negative tumors are positive with octreotide scintigraphy [58]. Primary or metastatic tumors expressing somatostatin receptors can be visualized with the help of radiolabeled somatostatin analogs. Expression of somatostatin receptors has been found in roughly 75% of PCCs [105]. While 111In-pentetreotide scintigraphy generally has a lower detection rate for malignant PCCs than 123I-MIBG scintigraphy [105–107], they can have a complementary role for the staging of malignant PCCs [105, 106, 108]. However, dedifferentiated tumors tend to have lower expression of somatostatin receptors [74, 90]. 111In-pentetreotide imaging appears to have a high sensitivity in detecting PGLs of the head and neck [109].

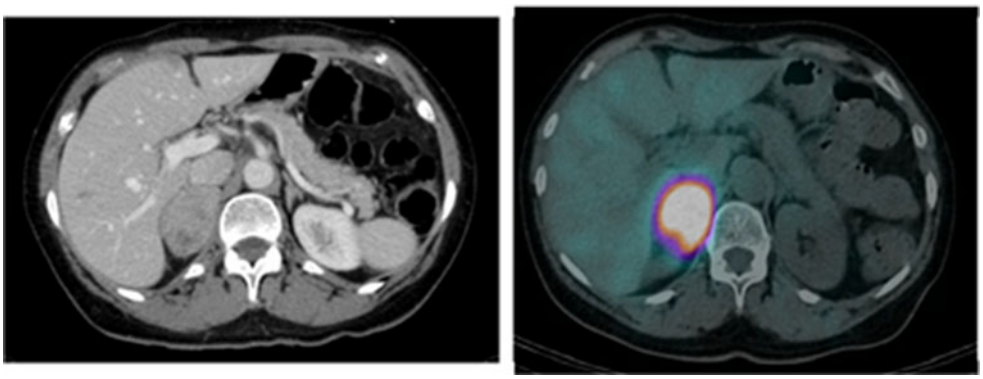

Fig. 1 CT (*left*) and 123I-MIBG SPECT-CT (*right*) in a right adrenal pheochromocytoma

The expression rate of somatostatin receptor in these tumors has been reported to be higher than 90% [105].

PET images

Because of growing clinical applications of positron emission tomography (PET), several PET radiopharmaceuticals have been developed in the exploration of neuroendocrine neoplasms such as [11C]hydroxyephedrine ([11C]HED), [11C] 5-hydroxytryptophan ([11C]HTP), [18F]fluoro-2-deoxy-D-glucose ([18F]FDG), [11C/18F]fluorodihydroxyphenylalanine ([11C/18F] FDOPA), [18F]fluorodopamine ([18F]FDA) and [68Ga]somatostatin-analogs ([68Ga]DOTA-TOC and [68Ga]DOTA-NOC) [87, 110–112].

11C-HED was the first positron-emitting probe of the sympathoedrenal system used in humans, and first results in the early 1990s were very promising. Due to the short half-time (about 20 min) of 11C, on-site production is required. Since the synthesis of 11C-HED is very complex, the need for other positron-emitting compounds was evident. 18F, having a half-time of about 110min, proved to be more promising.

In general, malignant and inflammatory tissues show increased uptake 18F-FDG due to increased glucose utilization [113]. This phenomenon has been investigated, improving both imaging and therapy of malignancies [114].

Concerning PCCs, the advantages of 18F-FDG in tumors that do not accumulate MIBG have been shown early [115]. It has been repeatedly shown that 18F-FDG PET imaging may be useful in those malignant PCCs that fail to accumulate either 123I-MIBG [116] or 131I-MIBG [117, 118]. One advantage of 18F-FDG in contrast to other tracers is that its uptake appears to be unrelated to the secretory status of the tumor. In patients with *SDHB*-associated PGLs/PCCs, 18F-FDG has been shown to be superior to 131I-MIBG, 123I-MIBG, 111In-pentetreotide and even 18F-FDA in detecting metastatic lesions [119].

Finally, 18F-FDG may have a prognostic role [79, 118].

Sodium 18F has been previously used for bone imaging and can be used as a PET skeletal tracer. A pilot study analyzing administration of combined 18FNa/18F-FDG showed promising results in metastatic PGLs [120]. Since only a single PET scan is needed, health care costs could be reduced.

18F-FDA, developed as a radiopharmaceutical agent for the detection of noradrenergic pathways, is difficult to produce and has limited availability [121]. Also, normal adrenal glands may give false-positive results. In this regard, the recent recommendation to the use of standardized uptake values (SUV) may be very helpful. If the SUV is <7.3, the presence of a PCC is very unlikely, while a SUV >10.1 confirms its presence [122–124]. In addition, 18F-FDA has been reported to be superior to MIBG in the localization of metastatic PCC [125]. In the case of bone metastases, 18F-FDA-PET was superior, followed by bone-scintigraphy, CT/MRI, 18F-FDG and 123/131I-MIBG [126].

18F-DOPA, which is incorporated into the cell via the amino acid transporter system, seems to have the advantage that there is no significant uptake in normal adrenal glands [127]. Its overall sensitivity and specificity concerning PCCs are high [128–130]. However, its sensitivity in metastatic PGLs is *low* [131]. This seems to be true also for malignant PCCs, where 18F-FDG appears to be more sensitive [132].

While PET with the 11β-hydroxylase tracer 11C-metomidate has been used successfully to discriminate between adrenocortical and non-adrenocortical lesions, it could not differentiate between benign and malignant diseases [133].

Recently, the introduction of 68Ga-labeled somatostatin analogues has enabled somatostatin imaging with PET agents [134]. In a small pilot-study analyzing patients with metastatic PCCs, 68Ga-DOTATATE proved to be superior to 123I-MIBG [135].

Development of MIBG analogues labeled with positron-emitting radionuclides such as 124I, 18F and 76Br has been also reported [103].

Biopsy

Biopsy of PCCs and/or PGLs is contraindicated because this invasive procedure has the risk of precipitating a hypertensive crisis, hemorrhage and tumor cell seeding [2, 136].

Summary

Most patients with malignant PCCs have the “typical signs” suggestive for PCCs: hypertension, palpitations, headache and diaphoresis. A lack of these “typical signs” or the presence of variable symptoms and signs, such as dyspnea, nausea, weakness, weight loss, visual disturbance, arrhythmias and mental problems, may raise the suspicion that one is dealing with a malignant tumor. Biochemically, high preoperative 24-h urinary dopamine levels (>5,000–6,000 nmol/24 h) and chromogranin A levels (>500–600 ng/mL) are suggestive but not proving that one might be dealing with a malignant tumor. Overall, it is considered that diagnosing patients with malignant tumors is more difficult when solely based on preoperative clinical and/or biochemical markers.

If PCCs are confined to the adrenal gland, both computed tomography (CT) and magnetic resonance imaging (MRI) have a very high sensitivity to identify the

lesion. CT of the abdomen should be performed first, followed by head and neck CT if the abdominal CT is negative [73]. In children and during pregnancy, MRI is recommended instead.

To confirm the presence of a PCC, some recommend a functional imaging technique in every patient [73]. In any case, functional imaging techniques are required when malignancy is suspected on other grounds. The most preferred method is 123I-MIBG scintigraphy, especially if imaging is correlated with SPECT-CT technique. However, MIBG may have lower performances in subsets of PCC patients, like some familial paraganglioma syndromes, malignant disease and extra-adrenal PGLs. In the case of negative MIBG scans, PET imaging with specific ligands is recommended [137]. While 18F-FDA is highly recommended [73, 138], 18F-FDG and other imaging techniques such as somatostatin receptor scintigraphy are more readily available and more commonly used. The sensitivity and specificity of various imaging techniques for PCCs and PGLs are shown in Tables 2 and 3. The estimated functional imaging performances for sporadic and various familial syndromes is shown in Table 4.

Therapy

Treatments for malignant PCCs include surgical resection, pharmacologic control of hormone-mediated symptoms, targeted methods such as external irradiation and systemic antineoplastic therapy [1, 5, 10, 11, 28]. The management of tumors in individuals with hereditary syndromes is similar to the management of sporadic tumors [58].

Surgery

Following preoperative treatment to block the effects of catecholamine excess (e.g. with α-adrenoceptor antagonists or channel blockers), surgery is the treatment of choice in almost all patients with PCCs and PGLs [1, 10, 12]. Basically, PCCs and PGLs can be divided into potentially malignant, suspicious malignant and overt malignant tumors. Overt malignant tumors are those with proven distant metastases [1, 11]. Suspicious malignant tumors are those with locoregional infiltration without distant metastases [1, 5, 11]. The remaining tumors are potentially malignant [1, 10, 11]. Surgical strategies differ between potentially malignant, suspicious malignant and overt malignant tumors [11].

For potentially malignant PCCs and PGLs, the surgical treatment follows the principle of benign diseases [1]. Local excision of the lesion usually performed by a minimally invasive approach is the accepted standard [139]. Partial adrenalectomy with complete removal of the PCCs may be indicated in bilateral and/or inherited diseases with low likelihood of malignancy, e.g. MEN2- or VHL-associated PCCs [140, 141]. In general, tumor capsular effraction should be avoided to prevent pheochromocytomatosis [142]. Regardless of tumor size, laparoscopic adrenalectomy for PCCs should be converted to open adrenalectomy for difficult dissection, invasion, adhesions or surgeon inexperience [139]. Data after minimally invasive removal of incidentally discovered malignant PCC are rare. Rabii and colleagues reported a case of a patient with a malignant PCC who underwent laparoscopic adrenalectomy followed by transperitoneal laparoscopic metastatic paraaortic lymph node resection 6 years later [143]. Walz and colleagues

Table 2 Pheochromocytomas (PCCs): sensitivity (%) and specificity (%) of various imaging techniques for detecting primary tumors and metastases

	Primary PCC				Metastases		References
	All PCC		Mal PCC				
	Sens	Spec	Sens	Spec	Sens	Spec	
CT	85–95	29–93			90		[57, 72–74]
MRI	65–95	50–93					[72–74, 77]
123I-MIBG	83–100	95–100	91		50–80		[72, 74, 87, 106, 135, 203, 204]
131I-MIBG	58–90	90–100	67–77				[78, 87, 204, 205]
111In-octreotide	75–90				44–88		[74, 78, 106]
18F-FDG	58		77				[204]
18F-DOPA	85	100					[128]
68Ga-DOTATATE					83		[135]

All PCC benign and malignant pheochromocytomas, *Mal PCC* malignant pheochromocytomas, *Sens* sensitivity, *Spec* specificity

Table 3 Paragangliomas (PGLs): sensitivity (%) and specificity (%) of various imaging techniques for detecting primary tumors and metastases

	Primary PGL				Metastases		References
	All PGL		Mal PGL				
	Sens	Spec	Sens	Spec	Sens	Spec	
CT	90–100	50			78–96		[73, 119, 126, 206]
MRI	100	50			78–95		[119, 126, 206]
111In-octreotide					<80		[105]
111In-pentetreotide					59–81		[119]
123-MIBG	98				65–80		[119, 126, 203]
131I-MIBG	50–82	100			30–71		[119, 126, 205, 206]
18F-FDG					76–100		[119, 126]
18F-FDA					70–90		[119, 126]

All PGL benign and malignant paragangliomas, *Mal PGL* malignant paragangliomas, *Sens* sensitivity, *Spec* specificity

removed four malignant PCCs by the posterior retroperitoneoscopic approach. One patient had skin metastases prior to adrenalectomy, two developed liver metastases within 3 years, and one patient had an interaortocaval lymph node metastasis 3 years postoperatively. Local recurrence was not observed in any of these cases [14].

Suspicious malignant cases should be treated by complete excision [12, 144]. This may include the resection of adjacent tissue and organs (liver, kidney, vena cava, spleen and pancreas) as the only curative option [1, 5, 11, 12, 58]. Unfortunately, locoregional invasion cannot usually be defined by preoperative imaging studies. Therefore, it has been recommended that potential invasive tumors should initially be explored by laparoscopy or retroperitoneoscopy followed by conversion to open surgery in case of critical adhesions [14, 144].

In patients with overt malignant PCCs (with distant metastases), surgery is palliative and tries to reduce the hormonal effects on the cardiovascular system by reduction of tumor tissue [1, 4]. Thereby, subsequent radiotherapy or chemotherapy may be facilitated [10].

Surgical treatment of PGLs follows the same principles as that for PCCs. Complete removal has to be achieved. This usually requires meticulous dissection from major vascular structures. Minimally invasive approaches have been demonstrated to be feasible and safe but must be categorized as advanced and challenging procedures [14, 145]. Therefore, open accesses are still the standard.

Non-surgical treatment modalities

MIBG

To date, 131I-labeled MIBG therapy is the single most valuable adjunct to surgical treatment of malignant PCC [10, 49]. As early as 1984, 131I-MIBG was administered in large doses for the treatment of malignant PCCs [11]. In a retrospective review of 33 patients with metastatic PCCs (n=22) or PGLs (n=11) treated over a 10-year period with 131I-MIBG, the median survival of patients was 4.7 years [146]. Approximately 60% of metastatic sites are 131I-MIBG avid, and in a recent meta-analysis including 166 patients, the objective response rate was 30%, and disease stabilization was achieved in an additional 43% of patients [49]. Recently, it has been reported that ultratrace iobenguane I-131 (Ultratrace 131I-MIBG) might provide improved efficacy and tolerability over carrier-added 131I-MIBG in the treatment of malignant PCCs [103, 147].

Finally, for potential use in the treatment of micrometastatic diseases, synthesis of an analogue labeled with the alpha emitter (211)At was devised [103].

Table 4 Estimated functional imaging performances (modified from [87])

	123I/131I-MIBG	Specific PET (18F-FDA/18F-DOPA)	Non-specific PET (18F-FDG)
Sporadic	+	++	++
MEN2	+	+	Insufficient data
VHL	(+)	++	Insufficient data
SDHB	+	++	++/++++
SDHC	Insufficient data	Insufficient data	Insufficient data
SDHD	+	Insufficient data	Insufficient data

Chemotherapy

Experience with cytotoxic chemotherapy is limited, and the best results were seen with a combination of cyclophosphamide, vincristine and dacarbazine (CVD) [148]. CVD showed varied success in several series, with survival benefit ranging from 1 to 4 years [11, 148]. In a 22-year follow-up study, there was no difference in overall survival between patients whose tumors objectively shrank and those with stable or progressive disease [148]. The authors conclude that CVD therapy is not indicated in every patient with metastatic PCCs/PGLs, but should be considered in the management of patients with symptoms and where tumor shrinkage might be beneficial [10, 148].

Up to now, no single-phase II or III trial investigating "new drugs" in malignant catecholamine-producing tumors has been published. More specific targeted therapy with imatinib mesylate has been tried with malignant PCCs, but no significant benefit was found [10]. The same holds true for everolimus, an inhibitor of mTOR that was not effective in four patients [10, 49]. The most promising but still immature results are reported with the multiple TKI sunitinib [10].

External radiation

External beam irradiation of bone metastases and other targeted methods (such as radiofrequency ablation of hepatic and other lesions, cryoablation, chemoembolization, cyber/gamma knife and arterial embolization) can help to alleviate local tumor complications and are treatment alternatives [10].

Recurrence

Even when seemingly complete, operative excision of malignant PCCs/PGLs does not preclude the later development of local-regional recurrence [149]. Several hypotheses for recurrent disease exist, including failure to identify and completely resect the primary tumor (especially if found in ectopic locations), tumor seeding (during needle biopsy or surgery) or the presence of metastases (nodes or distant) [11]. A recent study showed that recurrence can occur in nearly 25% of patients undergoing resection for an abdominal PGL, when followed up beyond 10 years after an apparently complete initial excision, which is a figure superior to those previously reported for PGLs in general [149]. In inherited syndromes, it is sometimes difficult to differentiate between local-regional recurrence and new ectopic locations. If the recurrence is determined resectable, reoperation remains the only option for cure but often represents a major technical challenge [11, 149]. Surgeons should also consider metastasectomy in organs where feasible, although it has not yet been determined if this will increase survival [150]. If recurrence presents as widespread metastases, then surgical excision is likely not an option. In those cases, systemic treatments as noted earlier will be the only option [11].

Summary

Surgery offers the only potential cure for malignant PCCs and PGLs but is rarely curative. The number of other supportive treatment modalities is very limited. Current research puts major efforts into identifying genes that contribute to the development of malignant PCCs and PGLs. Those genes may be targets for future therapeutic approaches.

Pathological aspects

The pathological diagnosis of malignancy in PCCs and PGLs remains a controversial issue [20, 151]: Nuclear hyperchromasia and pleiomorphism are common in these tumors but unrelated to their evolution. At the opposite, distant metastasis may occur up to 20 years after a histological diagnosis of benign PCC [7, 18, 29, 152–156]. Thus, there is a general feeling that histology is unable to predict the evolution of PCC [157]. The rarity, fluctuating definition and long evolution of malignant PCCs have been important limiting factors to the determination of histopathological criteria of malignancy: Locally invasive and metastasizing tumors were often analyzed indistinctly [8, 12, 158]. The mean follow-up period of benign PCC in studies exceeded scarcely 8 years, whereas the mean reported delay before the occurrence of metastasis was 8 to 12 years [8, 9, 154, 155, 159–164].

After a comprehensive analysis of the literature devoted to the pathology of malignant PCCs/PGLs (MEDLINE 1980–2010), we could find only four publications evaluating the gross and histopathological features of more than ten malignant cases with comparison to benign PCC followed at least 10 years [165–168]. Three other papers analyzed large numbers of malignant PCCs with lower mean follow-up periods for the benign control groups [158, 159, 169]. A series of differences were reported, with discrepancies about their significance, but there is a general agreement that no single parameter is pertinent enough to separate benign from malignant PCC. Then, scoring systems combining several variables were elaborated thereafter. In the main course, immunohistochemistry was used for assessment of malignant potential with disputable results.

Gross features

The mean size of malignant PCCs (8–9 cm) is greater than that of benign cases (4–5 cm), but authors agree that the size is not an independently helpful criterion to the diagnosis of malignancy [139, 166, 170]. Cystic degeneration and hemorrhage are not significant either.

Histological parameters

The histological parameters that have been analyzed in PCC fall under five categories: (1) architecture and cell-density: "Zellballen", large nest, diffuse architecture, high cellular density, cellular monotony and spindle cells (more than 10%); (2) invasiveness: in blood, lymphatic vessels, within capsule and into peri-adrenal adipose tissue; (3) cellular morphology: pleïomorphism, nuclear hyperchromasia and cytoplasmic hyaline globule; (4) cellular proliferation: mitotic count ≥3/10 HPF) and atypical form; and (5) degenerative changes: cystic changes and necrosis (focal or confluent).

Criteria concerning individual cellular morphology were poorly correlated to the malignant phenotype in most studies, whereas those concerning architecture were found significant almost constantly [8, 158, 169]. Vascular invasion exhibited borderline significance, and tumor invasiveness seems to reach significance when there is extensive invasion in the peri-adrenal tissue. Among degenerative changes, only confluent necrosis appears commonly useful, although its weight was diversely appreciated. The value of proliferative activity (mitotic count) was considered a useful criterion [166, 168] or not [158, 169], with cut-off values of 3/10 or 5/30 HPF, respectively. As discussed elsewhere, mitotic count can be difficult to interpret due to technical defects or pyknotic nuclei [151, 159]. The presence of atypical mitosis is highly significant but infrequent [166].

Multiparameter scoring systems

The model presented by Linnoila et al. in 1990 [158] used two gross features, i.e. extra-adrenal location and coarse nodularity, and two histological features, i.e. confluent necrosis and absence of cytoplasmic hyaline globules. It had an overall correct classification rate of 88% and enabled correct classification of 9 out of 12 clinically malignant PCCs and 20 out of 21 benign PCCs. In this model, the weight of the extra-adrenal location exceeded largely that of the other parameters. As the extra-adrenal location is linked to *SDH*x mutations and *SDH*x mutations are linked to malignancy [13], it can be anticipated that genetic testing will be more efficient than histopathology in predicting a malignant risk for extra-adrenal locations.

In 2002, Thompson developed a scaled score named pheochromocytoma of adrenal scaled score (PASS) (Table 5) made of 12 parameters weighted according to their relative frequency in benign and malignant adrenal PCCs [166]. A PASS of <4 accurately identified all benign tumors (50 cases clinically benign after a follow-up period >10 years). A PASS of ≥4 defined 50 histologically malignant tumors, of which 33 developed clinically malignant disease. The sensitivity of the PASS in this study was 100%, and the specificity was 75%. The PASS therefore was proposed to predict a benign course. At the opposite, a PASS ≥4 indicates a high risk of occurrence of metastasis but is not equivalent to a diagnosis of malignancy.

In 2005, Kimura et al. constructed a score using six clinical and histopathological features to characterize 116 adrenal PCCs and 30 extra-adrenal PGLs, of which 38 had metastasis: growth pattern, cellularity, necrosis, vascular/capsular invasion, Ki-67 immuno-reactivity and type of catecholamine [167]. Tumors were classified as well, moderately and poorly differentiated (WD, MD and PD) according to their scores. Metastases were observed in 13% of 113 WD, 63% of 27 MD and 100% of 6 PD. The respective 10-year survival was 83%, 38% and 0%. The main interest of this system is the correlation of the score with prognosis in malignant cases, but it is unable to predict a risk of malignant evolution in the WD group.

In 2006, the diagnostic performance of PASS evaluated by ROC curve analysis in 130 patients (48 malignant PCCs and 82 benign followed >10 years) was compared to a logistic regression model using 15 variables: Sex, age and

Table 5 Pheochromocytoma of adrenal gland scaled score (PASS) (according to [166])

Feature	Score if present (no. of points assigned)
Large nests or diffuse growth (> 10% of tumor volume)	2
Central (middle or large nests) or confluent tumor necrosis	2
High cellularity	2
Cellular monotony	2
Tumor cell spindling (even if focal)	2
Mitotic figures >3/10 HPF	2
Atypical mitotic figures	2
Extension into adipose tissue	2
Vascular invasion	1
Capsular invasion	1
Profound nuclear pleiomorphism	1
Nuclear hyperchromasia	1
Total	20

tumor size were added to the 12 criteria of the PASS score [168]. The Cohen' kappa value of these variables was >86%, confirming their reproducibility. The nine variables having the largest odd ratio were retained in the logistic model. The area under the ROC curve improved from 0,899 with PASS alone to 0,983 with the logistic model. This study confirmed the diagnostic interest of the PASS and showed that its performance might be improved through a different variable selection and weighting: Variables containing redundant information (diffuse growth/hypercellularity) or less reproducible criteria (nuclear pleiomorphism/hyperchromasia) might be removed.

The value of the PASS was confirmed in the study by Strong et al., where 32 of 43 benign adrenal PCCs had PASS <4 (74% specificity), whereas 5/5 malignant PCC had PASS ≥6 (100% sensitivity) [162]. In a study by Agarwaal et al., examining PASS in 93 patients, including 68 with a follow-up period of more than 5 years, as much as 27 of 84 (32%) benign cases showed a PASS >4, and the specificity was 68%, while five of five malignant adrenal PCCs had a PASS >4 (100%) [171]. In this study, a bladder malignant PCC had a PASS score of 2, confirming that this system should not be used for extra-adrenal tumors. The reproducibility of the PASS was addressed by a study among PCC experts that found significant interobserver and intraobserver variations in its assignment, and the experts concluded that it could not be currently recommended for clinical prognostication [163]. This study, however, included only two truly malignant cases (with distant metastasis), and 15 of the 52 benign cases had follow-up of less than 1 year. Moreover, some criteria were extracted from surgical reports instead of reviewing the slides, and four of the five pathologists attributed scores >4 to the majority of benign cases.

There is currently no agreement on the utility and reproducibility of the PASS scoring systems that still require validation in larger series of cases [20, 31, 150, 157]. Guidelines and templates provided by colleges of pathologists for reporting of adrenal tumors incorporate some of the elements of the PASS systems but not all [157]. At this timepoint, a high PASS score should not be considered as diagnostic of malignancy as some tumors with high score never metastasize. In an effort of standardization of pathological reports for prospective validation, it may be worthwhile analyzing separately all of the elements of the PASS score.

Immunohistochemistry

A large number of markers have been analyzed by immunohistochemistry in PCC, with discrepant results among investigators (reviewed in [151, 172]). In almost all of the studies, the level of correlation with malignancy, even if statistically significant, was never sufficient to have a diagnostic utility due to overlapping between benign and metastasizing tumors. Except for few markers, none of them was superior to standard histology to predict the malignancy of PCC. CD44s and telomerase reverse transcriptase hTERT [173, 174] showed a better discriminating power, but the results need further confirmation. The disappearance of pS100 positive sustentacular cells in malignant PCCs initially demonstrated by Lloyd in 1985 [175] has been confirmed in several studies [159, 166, 176, 177] and may be useful to underline diffuse growth areas, but it has no absolute value, as some metastasizing PCC may keep sustentacular cells. Finally, the Ki-67 proliferative index, extensively analyzed in PCC, remains the only marker whose interest seems largely accepted at the present time as no benign PCC had scores >2–3% [159, 162, 178, 179]. The counterpart of this high specificity, however, is a poor sensitivity as approximately 50% of malignant PCCs have a Ki-67 index below the 2–3% threshold value. The Ki-67 proliferation index is thus considered as a useful adjunct [162, 174].

Summary

PCCs and PGLs are rare tumors exhibiting a wide range of malignant phenotypes. Between the most common benign and obviously aggressive tumors, fatal in few years, exists a group of proliferations that follow a more progressive course characterized either by local invasiveness and relapse or by late distant metastasis: The creation of an intermediate group of borderline malignancy has been suggested for these tumors and might be clinically relevant. Actually, the histopathological diagnosis of the two first categories seems reliable, but becomes more uncertain in the borderline group. Significant histological parameters were determined, but none is diagnostic enough to be used alone to predict evolution. Among the multiparametric systems that have been developed, none is ready to be used in daily routine. If the PASS is used at the present time, it must be kept in mind that a high score will define a risk group but is not diagnostic of malignancy.

Molecular biomarkers predicting malignancy

As conventional histopathology/morphology is of little help in identifying malignant PCCs and PGLs, much effort has been invested into the identification of molecular markers that may help distinguishing benign from malignant tumors (Table 6). Analysis on the level of genes, epigenetic changes, RNA and protein expression has been performed mainly on tumor tissue.

Table 6 Genetic tumoral changes that may be helpful in differentiating malignant and benign PCCs and paragangliomas

Source	Investigated material	Results (malignant vs. benign/normal)	Reference
Human			
PCC	DNA/protein/RNA	Up: GNAS, INSM1, DOK5, ETV1, RET, NTRK1, …; down: TGIF1, DSC3, TNFRSF10B, RASSF2, …	[197]
PCC	MicroRNA	Over-expression: miR-483-5p; under-expression: miR-15a and miR-16	[196]
PCC	RNA/protein	>Twofold difference: 19 genes up-regulated; 113 down-regulated	[186]
PCC	Protein	Over-expression: c-erbB-2/Her2, Ki-67/MIB-1	[207]
PCC	Protein	Over-expression: SNAIL	[208]
PCC	Protein	Over-expression: SNAIL	[164]
PCC	Protein	Over-expression: c-erbB-2/Her2	[209]
PCC	RNA	>Twofold difference: 16 genes up-regulated; ca. 90 down-regulated	[187]
PCC	Protein	Over-expression: galectin-3	[210]
PCC	RNA	Under-expression: Secretogranin II, prohormone convertases (PC)1 and PC2, EM66	[211]
PCC	Protein/DNA	Over-expression of Ki-67/MIB-1; gain 17q; loss 1p, 3q	[174]
PCC	RNA	Over-expression: hTERT	[191]
PCC	Protein	High frequency of spindle-shaped cells detected by antibodies against chromogranin B and C	[212]
PCC	RNA/protein	Over-expression: hTERT; increased activity of telomerase	[173]
PCC	Protein/RNA	Over-expression: VEGF	[213]
PCC	RNA/protein	Up-regulation: HSP90, ETB, EPAS1, VEGF; down-regulation: EM66	[154]
PCC	Protein	Over-expression: N-cadherin	[214]
PCC	Protein/RNA	Over-expression: Cox-2	[215]
PCC	Protein	Over-expression: Tenascin	[216]
PCC	Protein	Expression of only one chromogranin A region in all malignant tumors	[194]
PCC	Protein	Over-expression: Ki-67/MIB-1	[217]
PCC	Protein	Over-expression: p53	[218]
PCC	Protein	Over-expression: ACTH; under-expression: NSE	[219]
PCC	Protein	Increased activity of telomerase	[190]
PCC	RNA	Increased activity of telomerase	[192]
PCC	Protein	Over-expression: Ki-67/MIB-1; under-expression: S-100	[179]
PCC	RNA/protein	Threefold up-regulation of c-myc	[220]
PCC/PGL	DNA	Malignant PCC: gain at 19q, trisomy 12; loss at 11q malignant PGL: gain at 1q	[184]
PCC/PGL	DNA	Higher intratumoral molecular heterogeneity for LOH	[185]
PCC/PGL	Protein	Over-expression: topoisomerase II alpha, Ki-67/MIB-1, under-expression: RB	[169]
Mouse			
PCC	Tumor-RNA	Metastatic phenotype, up: MAMDC2, JUB, MMP14, …; down: ZNF35, ASF1B, RIMS3, …	[200]

PCC pheochromocytoma, *Para* paraganglioma, *LOH* loss of heterozygosity

Tissue-based analysis of DNA

LOH analysis of familial PCC/PGL revealed a non-random association of genetic losses depending on the existing germline mutation. Losses of 1p and 3p are frequently found in both sporadic and MEN2-related PCCs, suggesting a common genetic etiology [180, 181]. In contrast, VHL-related PCCs have losses of chromosome 11 [182]. Head and neck PGLs show very few genomic copy number alterations, with a dominance of 11q deletions [183]. Using high-resolution whole-genome array comparative to genomic hybridization (CGH), recurrent genomic alterations in benign and malignant PCCs and PGLs have been identified [184]. It is of interest that DNA gain was significantly more often identified among malignant cases. Moreover, gain at 19q, trisomy 12 and loss at 11q were positively associated with malignant PCCs, while gain at 1q was commonly observed in the malignant PGLs. These results could speak in favor of malignant PCCs and malignant PGLs following different genetic pathways, as do their non-metastasizing counterparts.

Recently, a higher intratumoral heterogeneity for loss of heterozygosity (LOH) has been reported in malignant PCC/

PGL compared to benign tumors, underlining their different pathogenesis [185].

Tissue-based RNA genome wide analysis

Using microarray analysis of total RNA, a more than twofold difference in expression between benign and malignant PCs was reported in 132 genes, with the majority of them being down-regulated in malignant tumors [186]. In a similar study, another group identified slightly more than 100 genes to be differently expressed [187]. Again, in malignant PCC/PGL, the majority of the genes were down-regulated. Comparing the gene lists of both studies, only very few (e.g. QPCT (glutaminyl-peptide cyclotransferase), MAOA (monoamine oxidase) and DKK3 (Dickkopf homolog 3)) of the described genes were found in both studies. Despite the identification of numerous differently expressed genes, not a single gene has been identified, enabling a clear differentiation between malignant and benign tumors.

Tissue-based RNA/protein analysis of candidate genes

Numerous studies have aimed at defining prognostic biomarkers for detecting malignant PCC/PGL. Using RT-PCR and immunohistochemistry, a variety of such candidate genes and/or proteins have been found to be over-expressed (e.g. p53, c-erbB2/Her2, bcl-2, c-myc, Ki-67/MIB-1, EPAS1, ETB, VEGF, HSP90, Cox-2, Tenascin, N-cadherin, ACTH and SNAIL) or under-expressed (e.g. RB, EM66, S-100, NSE, Secretogranin II, prohormone convertases (PC)1 and (PC)2) in malignant versus benign PCCs/PGLs (Table 1). However, most of these markers remain at least controversial, and none could be convincingly confirmed by independent follow-up studies: While initially a high (40%) frequency of *p53* mutations in malignant PCCs was reported [187], this could not be confirmed [188].

Over-expression of c-erbB-2/Her2 has been reported by some authors to be associated with malignant PCCs [189]. In the same study, however, over-expression has also been reported in MEN2-associated PCCs that extremely rarely exhibit a malignant phenotype.

The significance of telomerase activity remains controversial. In one study, high telomerase activity was found in all malignant PCCs [190]. However, only three malignant tumors were investigated as opposed to 16 benign cases. In the same study, the telomerase catalytic subunit (hTERT) was also suggested as helpful, while the telomerase RNA component was not. These results could be confirmed by others [9, 173, 191]. In other/further studies, however, telomerase activity was only found in a minority of the malignant PCCs [192, 193]. Over-expression of HSP90 was described to be helpful in distinguishing between malignant (over-expression) and benign PCCs [154].

In one study, analyzing antibodies to various specific regions of the chromogranin A molecule showed immunoreactivity with antibodies to all regions examined in benign PCCs, whereas only one region was expressed in all malignant tumors [194].

Recently, the loss of SDHB expression detected by immunohistochemistry has been associated with a high risk of malignancy in a retrospective series of 60 consecutive PCC/PGL patients. This study only included sympathetic tumors, and head and neck PGLs were not analyzed [195].

Tissue-based analysis of epigenetic changes

The analysis of microRNA profiling in benign and malignant PCCs revealed an over-expression of miR-483-5p, while miR-15a and miR-16 were under-expressed [196]. Using the rat PCC cell line PC12, these mRNAs were found to regulate cell proliferation via their effect on cyclin D1 and apoptosis. Integrative epigenomic and genomic analysis has further revealed a variety of additional potential tumor suppressor genes (e.g. TGIF1, DSC3, TNFRSF10B and RASSF2) and oncogenes (e.g. GNAS, INSM1, DOK5, ETV1, RET and NTRK1) [197] involved.

Animal models

Since human PCC/PGL are rare and about 10% of these tumors are malignant, models for studying the process of malignant transformation are needed/necessary. Conditional *Pten* knock-out mice are used to investigate metastatic PCCs [198]. A spontaneous rat model with *p27* mutations develops PCCs with high proliferation rates. These tumors share expression profiles with human tumors and might be useful to understand the mechanism of tumor progression and therapy studies [199]. By comparing microarray gene expression of parental mouse PCC cells and more aggressive cells, several genes which may be important for this metastatic process have been identified, e.g. Fyn-related kinase (FRK) and keratin 8 (KRT8) (Table 1) [200]. In this model, however, the expression of many genes was very different in human tissues compared to mouse tissue, showing the difficulties of drawing direct conclusions from animal models.

Blood

None of the potential markers identified by molecular genetics has been convincingly shown to be a useful blood marker.

Summary

In summary, we are currently in the position of having a few more or less promising candidate markers to detect malignant PCC/PGL; none of them having been proven to be reproducible in a clinical setting, to our knowledge. In order to be useful (for indicating adjuvant therapy, for example), such a marker must prove very high specificity. Most of the studies are hampered due to the low number of investigated samples. At this point, no single marker has been identified enabling differentiation between malignant and benign PCCs/PGLs. Considering the genetic data, it might well be possible that different subtypes of PCC, sympathetic PGL and head and neck PGL will exist, with different risks and mechanisms of malignant transformation. It could be useful to introduce an intermediate category in the classification for those tumors exhibiting local aggressiveness at the time of diagnosis. It has also been proposed to abandon the term "malignant PCC/PGL" and just use the term PCC/PGL as has been done for melanomas [201]. PCCs/PGLs should instead be classified "non-invasive", "minimally invasive" or "extensively invasive" (the last two similarly to follicular thyroid carcinomas).

Concluding remarks

All of the recommendations given in this review can only be considered as level IV. Due to the rarity of malignant PCCs/PGLs and the obvious difficulties in distinguishing benign and malignant PCCs/PGLs, any patient with a PCC/PGL should be treated in a specialized center where a multidisciplinary setting with specialized teams consisting of radiologists, endocrinologist, oncologists, pathologists and surgeons is available [202]. This would also facilitate future studies to address the aforementioned diagnostic and/or therapeutic obstacles.

Conflicts of interest None.

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