We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800
Open access books available

122,000
International authors and editors

135M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities

CLARIVATE ANALYTICS BOOK CITATION INDEX INDEXED

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Chapter 5

Pheochromocytomas

Helen M. Heneghan and Ruth S. Prichard

Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/67373

Abstract

Pheochromocytomas are rare catecholamine-secreting neuroendocrine tumors derived from chromaffin tissue of the adrenal medulla. Such tumors arising from the sympathetic ganglia of the thorax, abdomen, or pelvis are termed "paragangliomas" or "extra-adrenal pheochromocytomas." The classic symptoms of these tumors are due to excess circulating levels of norepinephrine, epinephrine, or dopamine. Although 21% may be asymptomatic, the most common symptoms associated with pheochromocytomas include sweating, palpitations, and headaches in association with intermittent hypertension. If left untreated, excess catecholamines may result in hypertensive crisis leading to cardiac complications, cerebrovascular stroke, or ultimately sudden death. These catecholamine-secreting tumors are most commonly sporadic, but about 30% of patients have this disease as part of a familial disorder such as multiple endocrine neoplasia type 2 (MEN2) or von Hippel-Lindau (VHL) syndrome. Although most are benign, accurate recognition of pheochromocytomas with malignant potential and distant metastases remains a major diagnostic challenge. Advances in the field of molecular genetics have led to novel diagnostic and therapeutic strategies in an attempt to address this dilemma. Surgical excision of pheochromocytomas and paragangliomas is the mainstay of treatment and offers the only potential for cure. This chapter focuses on recent developments in the diagnosis of pheochromocytomas, encompassing biochemical, radiologic, histologic, and molecular analyzes. In addition, novel therapeutic strategies and advances in individualized targeted therapies for malignant pheochromocytomas will be discussed.

Keywords: pheochromocytoma, paraganglioma, diagnosis, management, therapeutics

1. Introduction

Pheochromocytomas are catecholamine-secreting tumors that arise from chromaffin cells of the adrenal medulla. Extra-adrenal pheochromocytomas or "paragangliomas" are those catecholamine-secreting tumors, which arise from the sympathetic ganglia. Whereas adrenal and extra-adrenal pheochromocytomas present and are treated similarly, the distinction between them is important for risk for malignancy, implications for associated neoplasms, and genetic testing. These rare neoplasms have an estimated annual incidence of approximately 0.8 per 100,000 person-years, and among people with hypertension in an outpatient setting, the prevalence varies between 0.2 and 0.6% [1–3]. Additionally, other tumors are discovered on autopsy such that the prevalence is likely to be underestimated [4]. The incidence of hereditary pheochromocytomas is estimated to be >30% in affected lineages [5]. Hereditary pheochromocytomas have been associated with >10 different germline mutations and are frequently a feature of a familial disorder or tumor syndrome, all of which have autosomal dominant inheritance (**Table 1**). They are also more likely to be malignant and bilateral than sporadic pheochromocytomas and present at younger ages.

Although pheochromocytomas may occur at any age, sporadic tumors are most common in the fourth to fifth decade, and there is no sex predilection [6]. The majority of pheochromocytomas and paragangliomas are benign and are associated with a normal life expectancy following treatment [7]. The incidence of malignancy is difficult to determine but ranges from 2.4 to 50% and higher among abdominal paragangliomas and those tumors harboring SDHB gene mutations [8–10]. Malignant pheochromocytomas often demonstrate local invasion, metastases, or recurrence and carry a worse prognosis with five-year survival rates of 20–70% [10–14].

Gene	Syndrome	Penetrance	Frequency of malignancy	PCC/PGL characteristics	Associated tumors
VHL	Von Hippel-Lindau	Autosomal dominant Variable expression	<10%	Young age (mean 28) Bilateral/multifocal	Retinal angiomas Hemangioblastoma Clear cell RCC
NF1	Neurofibromatosis	Autosomal dominant	<10%	Mean age 41 Bilateral disease common Extra adrenal PGL rare	Neurofibroma Neurofibrosarcoma Glioma Astrocytoma Carcinoid Leukemia
RET	MEN II	Autosomal dominant	<5% Extra-adrenal PGL rare	Mean age 40 Hyperparathyroidism No increased malignancy risk	Medullary thyroid cancer Mucosal neuromas
SDHC	PGL 3	Autosomal dominant	<5%	Mean age 46 Extra adrenal head & neck PGLs Bilateral/multifocal	Amyloidosis Cutaneous lichen GISTs

http://dx.doi.org/10.5772/67373

Gene	Syndrome	Penetrance	Frequency of malignancy	PCC/PGL characteristics	Associated tumors
SDHD	PGL 4	Autosomal dominant with parent of origin effect	<5%	Mean age 35 Extra adrenal head & neck PGLs Bilateral/multifocal	Papillary thyroid cancer GISTs
SDHB	PGL 1	Autosomal dominant	34–70%	Extra adrenal Increased malignancy risk Bilateral if adrenal	RCCs GISTs
SDHAF2	PGL 2	Autosomal dominant with parent of origin effect	Uncertain Head and neck PGLs	Extra adrenal	GISTs
TMEM 127		Autosomal dominant	5%	Adrenal Bilateral	
MAX		Autosomal dominant	10%	Adrenal Bilateral	

MEN, multiple endocrine neoplasia; PCC, pheochromocytoma; PGL, paraganglioma; RCC, renal cell carcinoma; GIST, gastrointestinal stromal tumor.

Table 1. Genetic mutations associated with pheochromocytomas and paragangliomas.

2. Clinical presentation

Since >50% of patients with pheochromocytomas are asymptomatic, these adrenal tumors are often identified as an "incidentaloma" on imaging studies obtained for other medical reasons or in patients with one of the hereditary syndromes of which pheochromocytomas are a feature. Symptoms reflect excessive secretion of norepinephrine, epinephrine, or dopamine into the circulation, and they are typically paroxysmal. The known triad of episodic headaches, sweating, and tachycardia occurs in about 40% of patients, although the majority will have two of these three classic symptoms [15]. Generalized sweating occurs in up to 70% of symptomatic patients. Other symptoms include palpitations, tremor, pallor, dyspnea, generalized weakness, and panic attack-type symptoms. Rarely, pheochromocytomas may present with a new diagnosis of diabetes, more commonly seen in younger patients who have no known risk factors. Approximately 50% of patients have paroxysmal hypertension, about 35–40% primary hypertension, and 10–15% are normotensive. A rare presentation due to an excess of circulating catecholamines, hypertensive crisis can precipitate life-threatening cardiovascular emergencies such as a myocardial infarction, cardiomyopathy, or a cerebrovascular accident in patients with pheochromoctyomas. Most common stimuli for eliciting hypertensive crises are exercise, tumor manipulation, and/or anesthesia, and for this reason, optimal preoperative and intraoperative management are essential [16].

Historically, pheochromocytomas and paragangliomas were thought to obey the "Rule of 10s": 10% malignant, 10% bilateral, 10% hereditary, 10% extra-adrenal, 10% children, 10% nonhypertensive,

and 10% calcified. However, this rule does not appear to hold true anymore, with recent advances in molecular biology demonstrating that >50% of tumors have a genetic link, 50% of tumors have malignant potential, and 25% of tumors arise in an extra-adrenal location [17].

3. Hereditary pheochromocytomas: genetics

Pheochromocytomas have the strongest genetic component of endocrine tumors with up to 50% being linked to germline and somatic mutations in 17 different genes [18]. The rate of genetic association is higher in children who develop pheochromocytomas with rates of up to 69% (**Table 1**) [19]. Other genetic conditions such as the Carney triad and Carney-Stratakis syndrome are known to be associated with development of paragangliomas, but the underlying gene has not yet been identified. Multiple endocrine neoplasia type 2 (MEN 2) syndrome, subclassified into MEN 2A and MEN 2B, is associated with mutations in the tyrosine kinase receptor proto-oncogene RET. Patients affected with MEN 2 typically present with medullary thyroid cancer (MTC), and 50% will also have or develop pheochromocytomas. While half of these patients will have bilateral tumors, malignant transformation is rare [13, 20]. Patients with known MEN 2 now commonly undergo prophylactic total thyroidectomy and have ongoing imaging surveillance for development of a pheochromocytoma. As with MEN 2, von Hippel Lindau (VHL) and neurofibromatosis type 1 (NF1) are characterized by a predisposition to multiple tumor types. The rate of pheochromocytoma development in NF1 is significantly lower than in VHL or MEN 2 syndromes; however, the metastatic rate for NF1-associated pheochromocytomas of approximately 12% is higher than with MEN 2 or VHL [21]. The Carney Syndrome (or Carney Complex) is a triad of tumors, which includes the development of paragangliomas. First described in 1977, this complex includes the occurrence of pulmonary chondroma, gastrointestinal stromal tumors, and functioning paragangliomas in affected young women [22]. Carney-Stratakis syndrome is the association of familial paraganglioma with gastric stromal sarcomas. It is considered to be a distinct condition from the Carney Complex as it is not associated with pulmonary chondroma, and it exhibits an autosomal dominant pattern of inheritance [23].

Up to 25% of apparent sporadic cases result from germline loss-of-function mutations in the genes encoding the subunits A[F2], B, C, and D of succinate dehydrogenase (SDH) [24–27]. The SDH enzyme is involved in the Krebs cycle, where it catalyzes the oxidation of succinate to fumarate and also in the respiratory electron transfer chain, where it transfers electrons to coenzyme-Q. Germline mutations in the SDH gene complex give rise to the hereditary paraganglioma (PGL) and pheochromocytoma syndromes of which there are four. These syndromes are termed PGL1, PGL2, PGL3, and PGL4 and are attributable to mutations in SDHD, SDHAF2, SDHC, and SDHB, respectively [28]. In addition, germline mutations in the SDH gene have been identified in other hereditary paraganglioma syndromes such as Carney-Stratakis syndrome [29], whereas SDHB mutations are found in approximately 1.7–6.7% of sporadic pheochromocytomas and linked to more aggressive thoracic or intra-abdominal paragangliomas with younger age of presentation, multiple tumors, and higher metastatic rates [30]. SDH-related tumors are typically extra-adrenal, although some cases of adrenal pheochromocytomas have been reported. These patients also have an increased risk of renal cell carcinoma, which can have a more aggressive phenotype earlier in life [31].

http://dx.doi.org/10.5772/67373

Due to rapid developments in molecular research over the past decade, several additional genes have been identified that contribute to hereditary pheochromocytomas. These include myc-associated factor X (MAX) mutations that have been identified in this gene in 1.12% of patients with no other known mutations [32], transmembrane protein 127 (TMEM127) [33], and most recently, hypoxia-inducible factor 2-alpha (HIF2A) [34]. Genetic testing in patients with pheochromocytomas is an important component of management, although not routinely performed in most sporadic cases, as it is both expensive and time-consuming. A study using next-generation sequencing of pheochromocytomas that analyzes multiple genes simultaneously has proven highly sensitive in detecting mutations and may provide clinically relevant data in the future [35]. More patients with pheochromocytomas are being referred for next-generation sequencing with the goal of optimizing surveillance protocols and identifying family members at risk of developing pheochromocytoma for screening.

4. Diagnosis

4.1. Biochemical investigation

The diagnosis of pheochromocytoma is primarily made through biochemical investigations with subsequent anatomic and functional imaging delineating extent of disease. Guidelines from the Endocrine Society, European Society of Endocrinology, and American Association of Clinical Endocrinologists recommend the measurement of plasma or urinary fractionated metanephrines (specifically, the O-methylated metabolites of catecholamines), as they are most accurate for diagnosis of pheochromocytoma, demonstrating excellent sensitivity (97%) and specificity (91%) [2]. Metanephrines are consistently elevated in patients with biochemically active or functional pheochromocytomas despite fluctuating catecholamine release. When measuring 24-hour urinary metanephrines, urinary creatinine should also be measured to verify completeness of urine collection. For plasma metanephrine measurement, it is recommended that patients be in the supine position at least 30 min before blood is drawn [2]. It is also important prior to testing that any substances that may cause false-positive elevations in urinary or plasma metanephrine levels are discontinued, which includes certain antihypertensives, antidepressants (particularly levodopa, tricyclic antidepressants, and selective serotonin reuptake inhibitors (SSRI)), and caffeine. If these ideal testing conditions are not met, false-positive rates can be as high as 41% [36]. Diagnostic levels of metanephrines for pheochromocytoma are defined as levels greater than three times the upper reference limit. In patients with elevated metanephrines, but to a level less than the diagnostic threshold, urinary collection for metanephrines should be repeated to ensure correct conditions as stated above. If equivocal levels are confirmed, further biochemical tests are required that include a clonidine suppression test, in which plasma normetanephrine levels will remain elevated in the presence of a functioning pheochromocytoma or paraganglioma [37]. In patients considered to be low risk for pheochromoctyomas, measuring plasma fractionated metanephrines is the first-line investigation as the predictive value of a negative test is extremely high and excludes such tumors, except in patients with early preclinical disease. If metanephrine levels are normal in asymptomatic patients, then no further evaluation is necessary unless patients have typical paroxysmal symptoms in which biochemical testing should be repeated during a spell. In this scenario, patients are instructed to start a 24-hour urine collection when they

have a typical spell. If results are still normal on repeat testing, other causes of spells should be investigated.

More recent studies have demonstrated the utility of plasma methoxytyramine in the diagnosis of pheochromocytoma, particularly for detecting exclusively dopamine-secreting tumors, which are rare and therefore can sometimes be overlooked by measuring only metanephrines [38, 39]. Chromogranin A, a polypeptide secreted by chromaffin cells, is the most accurate general biomarker for neuroendocrine tumors. Although not used in routine clinical practice, largely due to cost, chromogranin A is elevated in 91% of pheochromocytoma patients. While less specific, chromogranin A may be a valuable tool in monitoring response to treatment [40]. When chromogranin A is combined with catecholamine measurements, the sensitivity for diagnosis of pheochromocytoma approaches 100% and, in the majority of cases, normalizes after surgical resection of such tumors.

4.2. Radiologic studies

Once biochemical diagnosis of pheochromocytoma has been made, further evaluation with imaging is indicated to localize the primary tumor and assess for distant disease and allow for treatment planning including surgical resection. CT or MRI of the abdomen is initially performed to assess the adrenal gland. If these studies do not show an adrenal lesion in the presence of abnormal biochemical tests, then further imaging of the body is warranted [41]. CT and MRI are equally sensitive (98–100%) and specific (approximately 70%), and imaging choice depends upon cost, availability, and other issues such as radiation dose and use of contrast material. Historic concerns about contrast material provoking catecholamine release, and hypertensive crises have not been borne out in the literature; nonionic or low-osmolar contrast-enhanced CT is considered safe and does not require pretreatment with alpha- and beta-blockade [42]. The Endocrine Society recommends CT as the first-choice imaging modality because of its excellent spatial resolution for thorax, abdomen, and pelvis (**Figure 1**). MRI is the imaging modality of choice in patients with metastatic disease, head, and neck paragangliomas, CT-contrast allergies, pregnant women, children, and patients in whom radiation exposure should be limited (**Figure 2**) [2].

Functional imaging including metaiodobenzylguanidine scintigraphy (MIBG), positron emission tomography (PET), or somatostatin receptor imaging may also be required to evaluate the extent of disease, looking predominantly for extra-adrenal glands, and to accurately stage patients. Functional imaging is also indicated when abdominal CT or MRI is negative in the presence of clinical and biochemical evidence of pheochromocytoma. MIBG scintigraphy, using the catecholamine precursor 123I- or 131I-metaiodobenzylguanidine that is taken up by adrenergic tissue, is the first-line functional imaging modality. MIBG is a compound resembling norepinephrine that is taken up by adrenergic tissue. MIBG can identify tumors not detected by CT or MRI, in addition to localizing multiple or extra-adrenal tumors when CT or MRI abdomen is positive (**Figure 3**). Overall reported sensitivity and specificity of MIBG scanning is 94 and 92%, respectively [20]. Patients taking certain medications including tricyclic antidepressants, labetalol, and specific calcium antagonists should temporarily discontinue these drugs prior to scanning as they may interfere with 123I-MIBG uptake and image interpretation. 123I-MIBG has superior imaging quality than 131I-MIBG, and it is the radiotracer of choice when available

http://dx.doi.org/10.5772/67373

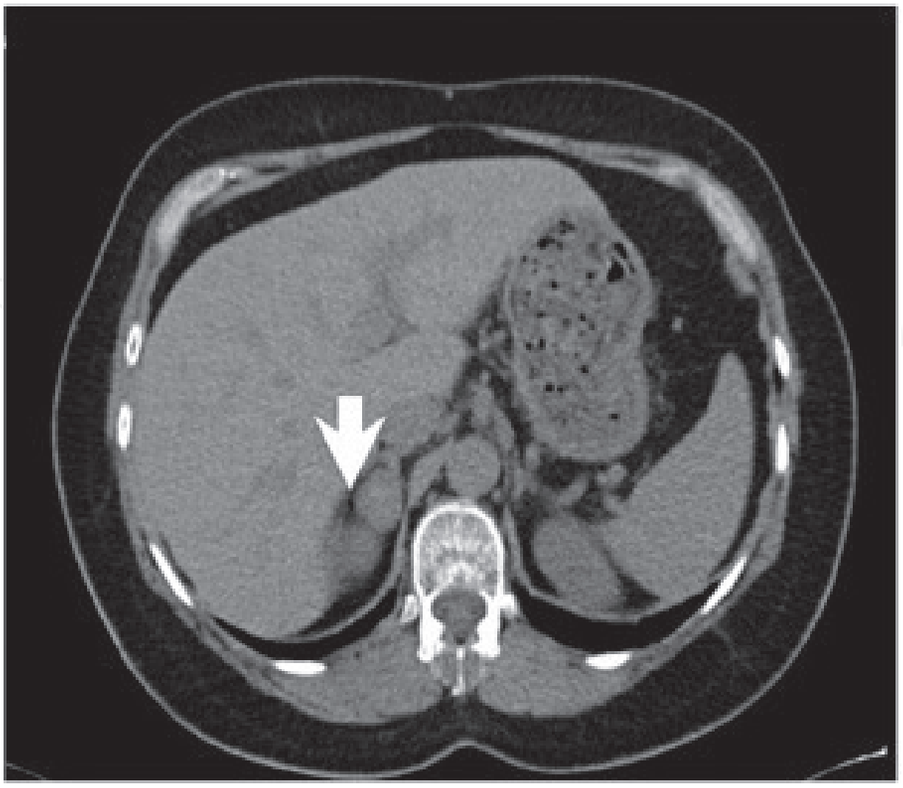

Figure 1. Axial CT imaging of a right adrenal heterogeneous mass measuring 34 hounsfield units on noncontrast phase. On enhanced and delayed series, the mass demonstrated relatively little washout and CT features are consistent for a pheochromocytoma.

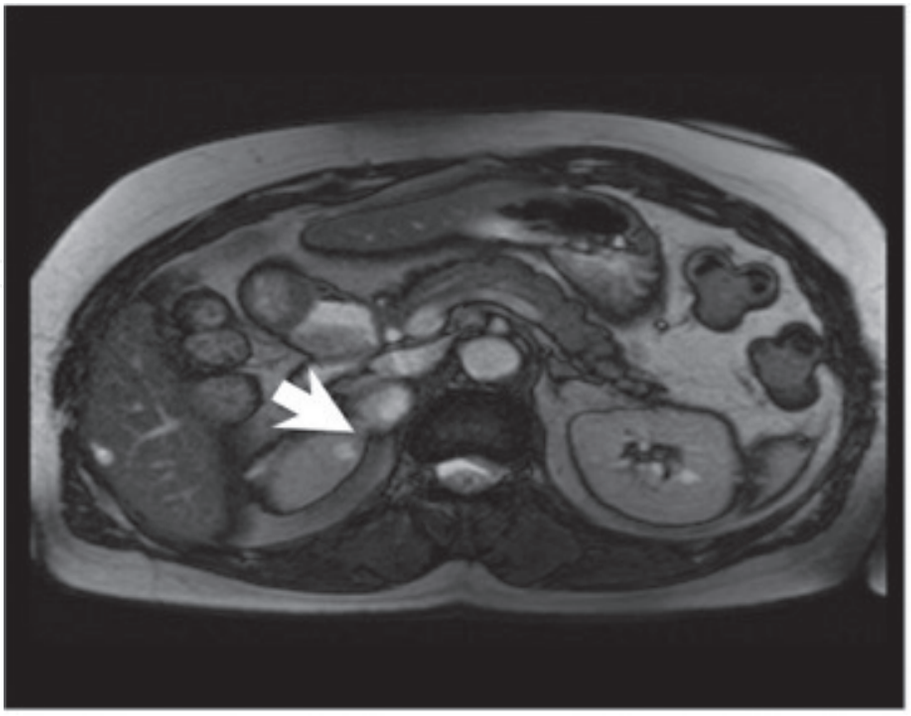

Figure 2. Axial MRI showing a mass (*white arrow*) in the medial limb of the right adrenal gland with a heterogeneously high signal on T2-weighted imaging consistent for a pheochromocytoma.

[43, 44]. A note of caution with regard to MIBG imaging is that its sensitivity is decreased in malignant pheochromocytomas [45]. This may be due to reduced expression of norepinephrine transporters in malignant adrenal tumors or dedifferentiation. It has been shown that tumors associated with VHL and SDHB genetic mutations may express a reduced number of noradrenaline transporters and, therefore, are more likely to be negative on MIBG imaging [46, 47].

Single-photon emission computed tomography (SPECT) imaging has been used in combination with both CT and MRI to increase accuracy in tumor localization as it involves simultaneous acquisition of both morphologic and functional data (**Figure 4**). However, SPECT imaging can miss smaller lesions due to relatively low resolution. Positron emission tomography (PET), using biologically active tracer-labeled molecules (18F-flurodeoxyglucose (FDG) most commonly), is increasingly employed in the diagnostic workup of pheochromocytomas and paragangliomas, particularly in patients where MIBG is negative. Although the 18F-FDG tracer is not specific for pheochromocytomas, it is useful in detecting pheochromocytomas and paragangliomas that do not accumulate MIBG, and it is superior to other functional imaging techniques in patients with disease associated with SDHB mutations [46]. The Endocrine Society guidelines favor [18F-FDG] PET-CT as the preferred imaging modality over 123I-MIBG scintigraphy in patients with known metastatic disease [2]. Recently, more specific tracers including 18F-DOPA, 18F-FDA (fluorodopamine), and 11C-HED (metahydroxephedrine) have been developed for pheochromocytoma and paraganglioma functional imaging but are not yet widely available.

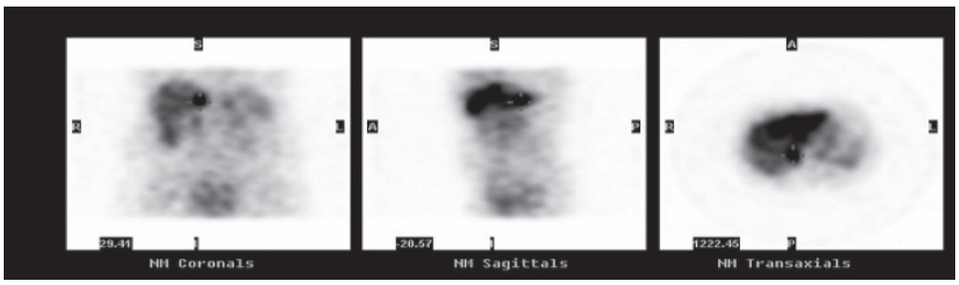

Figure 3. ^{123}I-MIBG scan showing focal uptake in the right adrenal gland consistent for a pheochromocytoma.

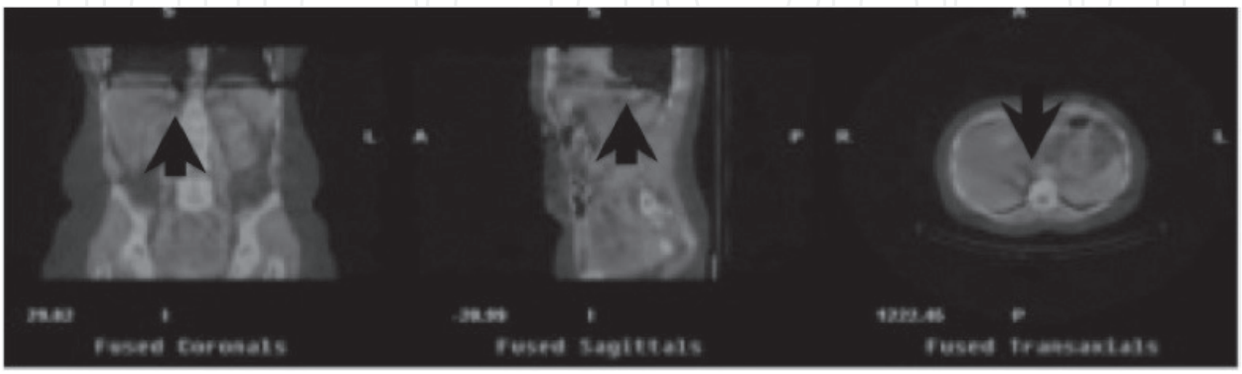

Figure 4. SPECT/CT imaging demonstrates focal tracer uptake in the right suprarenal region (*arrow*) suspicious for a right adrenal pheochromocytoma.

Image-guided needle biopsy of suspected pheochromocytomas should be avoided due to a high rate of biopsy-related complications such as triggering hypertensive crises, hematoma, severe pain, incorrect or inadequate biopsy, increased difficulty of surgical resection, and delay to definitive surgical treatment [48].

4.3. Histopathologic diagnosis of pheochromocytoma

The histologic diagnosis of pheochromocytomas is rather uncomplicated but difficulty arises when differentiating benign from malignant tumors. Tumor cells in pheochromocytomas and paragangliomas demonstrate a typical nested Zellballen pattern surrounded by sustentacular cells, which stain positive for S100 protein on immunohistochemistry. Characteristically, they exhibit immunopositivity for synaptophysin and chromogranin A and may express neurofilament [49]. There are no absolute histologic criteria for the diagnosis of malignancy and no reliable means to identify patients with pheochromocytomas who are at the risk of recurrence or metastatic spread using standard histopathologic techniques. Several histologic scoring systems have been devised to guide pathologists in the diagnosis of malignancy. The pheochromocytoma of the adrenal gland scoring system (PASS), devised by Thompson in 2002, is the most commonly used system (**Table 2**) [50]. In PASS, the histologic features of each pheochromocytoma are given a score, and the sum score is used to stratify the tumors into groups with potential for aggressive behavior (PASS > 4) and those likely to behave in a benign manner (PASS < 4). It is recommended that any patient with a PASS score of >4 should be closely followed [51]. However, this scoring system has limitations. It has been shown to have significant interobserver and intraobserver variation leading to recommendations that it be used with caution.

Features	Score
Large nest of cells or diffuse growth >10% of tumor volume	2
Necrosis (confluent or central in large nests)	2
High cellularity	2
Cellular monotony	2
Presence of spindle shaped tumor cells	2
Atypical mitotic figures (>3 per 10 high power fields)	2
Extension of tumor into adjacent fat	2
Vascular invasion	1
Capsular invasion	1
Profound nuclear pleomorphism	1
Nuclear hyperchromasia	1
A PASS score of <4 suggest a pheochromocytoma likely to behave in a benign manner [50].	
A PASS score of ≥4 indicates a tumor with potentially aggressive behavior (PASS ≥ 4).	

Table 2. Pheochromocytoma of the adrenal gland scoring scale (PASS).

Although several immunohistochemical markers of malignancy for pheochromocytomas have been proposed, none have emerged as reliable candidates for routine use in clinical practice. Markers that have been investigated to date include neuroendocrine-related and catecholamine-related markers (neuropeptide Y, 3,4-dihydroxyphenylalanine), granin-derived peptides (EM66, secretogranin II), CD-44s, angiogenic markers, and regulators (vascular endothelial growth factor (VEGF) and VEGFR), heat shock protein 90, and telomerase complex proteins.

5. Treatment

The curative treatment of choice for pheochromocytomas is surgical resection. However, management of some pheochromocytomas (particularly malignant, metastatic, or recurrent tumors) requires a multimodal therapeutic approach including pharmacologic control of catecholamine-mediated symptoms, radiotherapy, and systemic chemotherapy [52].

5.1. Pharmacologic management

Antihypertensive medications should be initiated in patients with biochemically active pheochromocytomas, not only to manage symptoms, but also to reduce the risk of a hypertensive crisis that can have devastating consequences. Initial pharmacologic management involves alpha-adrenoceptor blockers (e.g., long-acting phenoxybenzamine or short-acting prazosin, terazosin, or doxazosin) followed by cardioselective beta-blockade (e.g., metoprolol or atenolol) when necessary for reflexive tachycardia. It is important not to initiate beta-blockers before alpha blockade as this can lead to unopposed stimulation of alpha-adrenoceptors resulting in a hypertensive crisis [53]. Other hypertensive medications including calcium channel blockers are occasionally prescribed for patients with refractory hypertension, as single agents in patients with mild hypertension or in those who cannot tolerate alpha blockade [54].

5.2. Pre-operative care

All patients with a known pheochromocytoma who are scheduled to undergo surgical resection should have an extensive preoperative evaluation to exclude underlying metastatic disease that, if present, may influence treatment approach. Preoperative pharmacologic blockade using appropriate antihypertensive medication and careful fluid resuscitation is imperative to reduce the possibility of intraoperative hypertensive crises [55]. It is recommended that even patients who are normotensive preoperatively should receive alpha and possible beta-blockade, as unanticipated catecholamine release by the tumor during surgery may still precipitate hypertensive crisis [53]. As the alpha-blocker dose is increased, patients should start to have symptoms such as stuffy nose, fatigue, and mild postural hypotension that reflect adequate blockade. All patients should have a comprehensive anesthetic clearance preoperatively to assess cardiorespiratory fitness for surgery. Endocrine

http://dx.doi.org/10.5772/67373

Society guidelines recommend a high sodium diet along with sufficient fluid intake to reverse catecholamine-induced blood volume contraction preoperatively to prevent severe hypotension following tumor removal [2]. Cardiovascular parameters and blood glucose should also be carefully monitored perioperatively.

5.3. Adrenalectomy

Adrenalectomy is the treatment of choice for pheochromocytomas [56]. A laparoscopic surgical approach is the current preferred technique when technically feasible (**Figure 5**). It is associated with shorter length of stay, decreased analgesic requirements, and increased patient satisfaction [9, 57]. There is no consensus yet with respect to the superior laparoscopic approach—transperitoneal or retroperitoneal; the choice is determined by the surgeon's experience and preference. In patients with bilateral pheochromoctyomas or those at risk of bilateral disease due to known syndromes such as MEN2 or VHL, bilateral cortical sparing adrenalectomy has been proposed [58]. It is important to consider underlying genotype when selecting patients suitable for cortical sparing adrenalectomy as patients with MEN-2A or VHL mutations have a high risk of bilateral tumors yet low rates of malignancy, whereas patients with SDHB mutations should undergo total adrenalectomy carried out due to the increased risk of malignancy associated with these mutations. Patients with extensive locoregional infiltration from malignant pheochromocytomas usually require an open procedure to remove the tumor and any involved organs *en bloc*. For patients in whom safe curative surgical excision is deemed impossible, debulking/cytoreductive surgery can improve symptoms caused by local invasion. For patients with benign pheochromocytomas, surgical excision alone is curative. However, for patients with suspected or confirmed metastatic disease, alternative or additional treatment modalities may be required.

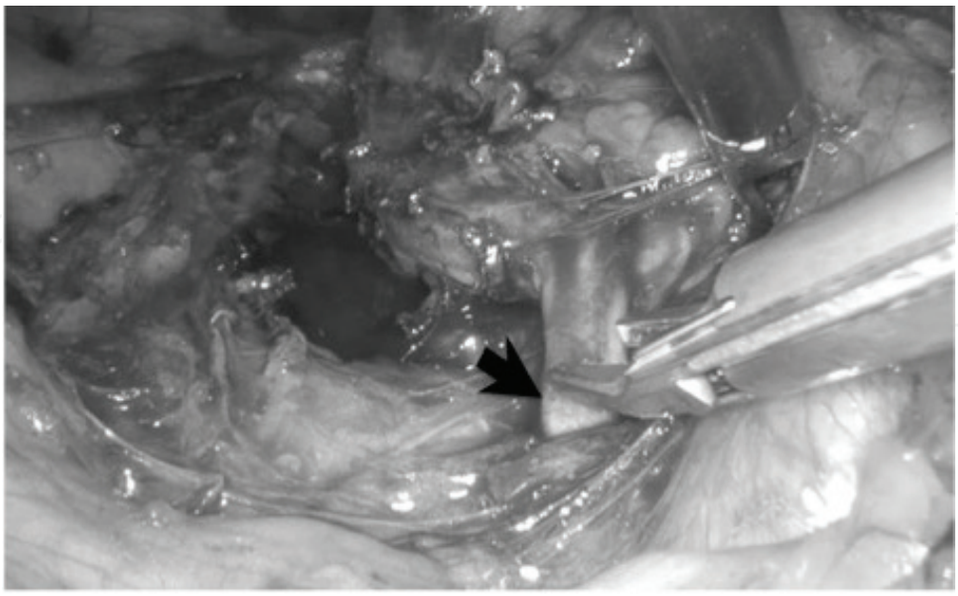

Figure 5. Transperitoneal laparoscopic left adrenalectomy showing the left adrenal vein (*arrow*) dissected prior to ligation.

5.4. Radiotherapy

Although malignant pheochromocytomas have limited radiosensitivity, patients with metastatic disease and those unsuitable for surgical intervention may be candidates for radiotherapy. Radiofrequency ablation and external beam radiotherapy are modalities in current use [59]. Radiotherapy is also used in the treatment of unresectable head and neck paragangliomas where long-term control can be obtained with limited toxicity [60]. When used in conjunction with radionuclide therapy (131I-MIBG), external radiation has been shown to improve response rates in a small number of patients with widespread systemic metastases [61].

5.5. Radionuclide therapy

Radionuclide treatment is indicated for patients with malignant disease in whom surgery is not a feasible option. Based on administration of radioactive compounds leading to the emission of beta particles into tumor cells causing their destruction, these beta-emitting isotopes are coupled to either 131I-MIBG or somatostatin analogs that allow uptake into chromaffin cells of adrenergic tissue. Patients with metastatic disease with 131I-MIBG uptake on imaging may be suitable for this treatment modality.

5.6. Chemotherapy

Malignant pheochromocytomas are not particularly chemosensitive. Chemotherapy is largely reserved for those patients not amenable to surgical therapy and who do not respond to radionuclide treatment. The most common regimen of cyclophosphamide, vincristine, and dacarbazine (CVD) has been shown to be of some value in palliating symptoms of advanced disease, reducing the rate of tumor growth, and occasionally decreasing tumor size [62, 63]. Experience with alternative chemotherapeutic agents for pheochromocytomas is limited and mostly based on isolated case reports and small series. Further, clinical trials are needed before recommendations can be made on their use in pheochromocytomas and paragangliomas [64].

5.7. Targeted therapy

Since standard adjuvant therapies have been demonstrated to have limited efficacy in treating advanced pheochromocytomas, newer therapeutic targets are currently being studied. Underlying genetic mutations and molecular alterations associated with malignancy have led to the identification of molecular therapeutic targets that include the mammalian rapamycin (mTOR) protein kinase, which is known to be upregulated in malignant pheochromocytomas [65], angiogenesis-mediated growth factors such as vascular endothelial growth factor (VEGF) and heat shock protein 90 (Hsp90), which are also overexpressed in malignant pheochromocytomas [66]. The mTOR inhibitor, Everolimus, has been used in a number of patients with malignant pheochromocytomas, but results have been disappointing [67]. This may be due to compensatory P13K/AKT and ERK activation in response to mTOR inhibition [68]. Further studies of targeting more than one pathway to overcome drug resistance are in progress using a combination of mTOR inhibition with other specific molecular drugs.

Like other tumors, targeting angiogenesis-mediated tumor growth by the VEGF pathway has been evaluated in the treatment of malignant pheochromocytoma. Sunitinib, a tyrosine kinase inhibitor that inhibits VEGF-R, PDGF, and c-KIT, was originally developed as a treatment for renal cell carcinoma but has shown some promising results for malignant pheochromocytomas with reduction in tumor size, catecholamine secretion, and metabolic activity on functional imaging [69]. Additional targets for therapy of pheochromocytomas will be identified with increasing understanding of tumor pathogenesis.

6. Summary

With the advent of improved diagnostic imaging and a greater understanding of molecular genetics, an increasing number of patients with pheochromocytomas are being identified. The majority of these patients have benign disease that can be cured by minimally invasive surgical resection. The recognition of malignant potential remains a major diagnostic challenge, and the presence of metastatic disease still carries a poor prognosis. Several targets for therapy have been already identified for further evaluation, which may offer promising therapeutic options in the future.

Author details

Helen M. Heneghan and Ruth S. Prichard*

*Address all correspondence to: ruthprichard@rcsi.ie

Department of Endocrine Surgery, St. Vincent's University Hospital, Dublin, Ireland

References

[1] Beard CM, Sheps SG, Kurland LT, Carney JA, Lie JT. Occurrence of pheochromocytoma in Rochester, Minnesota, 1950 through 1979. Mayo Clin Proc. 1983;58(12):802–4.

[2] Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915–42.

[3] Omura M, Saito J, Yamaguchi K, Kakuta Y, Nishikawa T. Prospective study on the prevalence of secondary hypertension among hypertensive patients visiting a general outpatient clinic in Japan. Hypertens Res Off J Jpn Soc Hypertens. 2004;27(3):193–202.

[4] Sutton MG, Sheps SG, Lie JT. Prevalence of clinically unsuspected pheochromocytoma. Review of a 50-year autopsy series. Mayo Clin Proc. 1981;56(6):354–60.

[5] Gimenez-Roqueplo AP, Dahia PL, Robledo M. An update on the genetics of paraganglioma, pheochromocytoma, and associated hereditary syndromes. Hormone and

Metabolic Research = Hormon- und Stoffwechselforschung = Hormones et metabolisme. 2012;44(5):328–33.

[6] Guerrero MA, Schreinemakers JM, Vriens MR, Suh I, Hwang J, Shen WT, et al. Clinical spectrum of pheochromocytoma. J Am Coll Surg. 2009;209(6):727–32.

[7] Timmers HJ, Brouwers FM, Hermus AR, Sweep FC, Verhofstad AA, Verbeek AL, et al. Metastases but not cardiovascular mortality reduces life expectancy following surgical resection of apparently benign pheochromocytoma. Endocr Relat Cancer. 2008; 15(4):1127–33.

[8] Proye C, Vix M, Goropoulos A, Kerlo P, Lecomte-Houcke M. High incidence of malignant pheochromocytoma in a surgical unit. 26 cases out of 100 patients operated from 1971 to 1991. J Endocrinol Invest. 1992;15(9):651–63.

[9] Walz MK, Alesina PF, Wenger FA, Koch JA, Neumann HP, Petersenn S, et al. Laparoscopic and retroperitoneoscopic treatment of pheochromocytomas and retroperitoneal paragangliomas: results of 161 tumors in 126 patients. World J Surg. 2006;30(5):899–908.

[10] Chrisoulidou A, Kaltsas G, Ilias I, Grossman AB. The diagnosis and management of malignant phaeochromocytoma and paraganglioma. Endocr Relat Cancer. 2007;14(3):569–85.

[11] Nomura K, Kimura H, Shimizu S, Kodama H, Okamoto T, Obara T, et al. Survival of patients with metastatic malignant pheochromocytoma and efficacy of combined cyclophosphamide, vincristine, and dacarbazine chemotherapy. J Clin Endocrinol Metab. 2009;94(8): 2850–6.

[12] Sisson JC, Shulkin BL, Esfandiari NH. Courses of malignant pheochromocytoma: implications for therapy. Ann N Y Acad Sci. 2006;1073:505–11.

[13] Tischler AS. Pheochromocytoma: time to stamp out "malignancy"?. Endocr Pathol. 2008;19(4):207–8.

[14] Zarnegar R, Kebebew E, Duh QY, Clark OH. Malignant pheochromocytoma. Surg Oncol Clin N Am. 2006;15(3):555–71.

[15] Soltani A, Pourian M, Davani BM. Does this patient have pheochromocytoma? a systematic review of clinical signs and symptoms. J Diabetes Metab Disord. 2015;15:6.

[16] Brouwers FM, Lenders JW, Eisenhofer G, Pacak K. Pheochromocytoma as an endocrine emergency. Rev Endocr Metab Disord. 2003;4(2):121–8.

[17] Madani R, Al-Hashmi M, Bliss R, Lennard TW. Ectopic pheochromocytoma: does the rule of tens apply?. World J Surg. 2007;31(4):849–54.

[18] Martucci VL, Pacak K. Pheochromocytoma and paraganglioma: diagnosis, genetics, management, and treatment. Curr Probl Cancer. 2014;38(1):7–41.

[19] Cascon A, Inglada-Perez L, Comino-Mendez I, de Cubas AA, Leton R, Mora J, et al. Genetics of pheochromocytoma and paraganglioma in Spanish pediatric patients. Endocr Relat Cancer. 2013;20(3):L1–6.

[20] Bombardieri E, Giammarile F, Aktolun C, Baum RP, Bischof Delaloye A, Maffioli L, et al. 131I/123I-metaiodobenzylguanidine (mIBG) scintigraphy: procedure guidelines for tumour imaging. Eur J Nucl Med Mol Imaging. 2010;37(12):2436–46.

[21] Karasek D, Shah U, Frysak Z, Stratakis C, Pacak K. An update on the genetics of pheochromocytoma. J Hum Hypertens. 2013;27(3):141–7.

[22] Carney JA, Sheps SG, Go VL, Gordon H. The triad of gastric leiomyosarcoma, functioning extra-adrenal paraganglioma and pulmonary chondroma. N Engl J Med. 1977;296(26):1517–8.

[23] Carney JA, Stratakis CA. Familial paraganglioma and gastric stromal sarcoma: a new syndrome distinct from the Carney triad. Am J Med Genet. 2002;108(2):132–9.

[24] Astuti D, Douglas F, Lennard TW, Aligianis IA, Woodward ER, Evans DG, et al. Germline SDHD mutation in familial phaeochromocytoma. Lancet. 2001;357(9263):1181–2.

[25] Baysal BE, Ferrell RE, Willett-Brozick JE, Lawrence EC, Myssiorek D, Bosch A, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. Science. 2000;287(5454):848–51.

[26] Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, et al. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med. 2002;346(19):1459–66.

[27] Peczkowska M, Cascon A, Prejbisz A, Kubaszek A, Cwikla BJ, Furmanek M, et al. Extra-adrenal and adrenal pheochromocytomas associated with a germline SDHC mutation. Nat Clin Pract Endocrinol Metab. 2008;4(2):111–5.

[28] Ricketts C, Woodward ER, Killick P, Morris MR, Astuti D, Latif F, et al. Germline SDHB mutations and familial renal cell carcinoma. J Natl Cancer Inst. 2008;100(17):1260–2.

[29] Pasini B, McWhinney SR, Bei T, Matyakhina L, Stergiopoulos S, Muchow M, et al. Clinical and molecular genetics of patients with the Carney-Stratakis syndrome and germline mutations of the genes coding for the succinate dehydrogenase subunits SDHB, SDHC, and SDHD. Eur J Hum Genet. 2008;16(1):79–88.

[30] van Hulsteijn LT, Dekkers OM, Hes FJ, Smit JW, Corssmit EP. Risk of malignant paraganglioma in SDHB-mutation and SDHD-mutation carriers: a systematic review and meta-analysis. J Med Genet. 2012;49(12):768–76.

[31] Gill AJ, Pachter NS, Clarkson A, Tucker KM, Winship IM, Benn DE, et al. Renal tumors and hereditary pheochromocytoma-paraganglioma syndrome type 4. N Engl J Med. 2011;364(9):885–6.

[32] Burnichon N, Cascon A, Schiavi F, Morales NP, Comino-Mendez I, Abermil N, et al. MAX mutations cause hereditary and sporadic pheochromocytoma and paraganglioma. Clin Cancer Res. 2012;18(10):2828–37.

[33] Qin Y, Yao L, King EE, Buddavarapu K, Lenci RE, Chocron ES, et al. Germline mutations in TMEM127 confer susceptibility to pheochromocytoma. Nat Genet. 2010;42(3):229–33.

[34] Zhuang Z, Yang C, Lorenzo F, Merino M, Fojo T, Kebebew E, et al. Somatic HIF2A gain-of-function mutations in paraganglioma with polycythemia. N Engl J Med. 2012;367(10):922–30.

[35] Rattenberry E, Vialard L, Yeung A, Bair H, McKay K, Jafri M, et al. A comprehensive next generation sequencing-based genetic testing strategy to improve diagnosis of inherited pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2013;98(7):E1248–56.

[36] Eisenhofer G, Goldstein DS, Walther MM, Friberg P, Lenders JW, Keiser HR, et al. Biochemical diagnosis of pheochromocytoma: how to distinguish true- from false-positive test results. J Clin Endocrinol Metab. 2003;88(6):2656–66.

[37] Eisenhofer G, Siegert G, Kotzerke J, Bornstein SR, Pacak K. Current progress and future challenges in the biochemical diagnosis and treatment of pheochromocytomas and paragangliomas. Horm Metab Res. 2008;40(5):329–37.

[38] Eisenhofer G, Goldstein DS, Sullivan P, Csako G, Brouwers FM, Lai EW, et al. Biochemical and clinical manifestations of dopamine-producing paragangliomas: utility of plasma methoxytyramine. J Clin Endocrinol Metab. 2005;90(4):2068–75.

[39] Poirier E, Thauvette D, Hogue JC. Management of exclusively dopamine-secreting abdominal pheochromocytomas. J Am Coll Surg. 2013;216(2):340–6.

[40] Grossrubatscher E, Dalino P, Vignati F, Gambacorta M, Pugliese R, Boniardi M, et al. The role of chromogranin A in the management of patients with phaeochromocytoma. Clin Endocrinol (Oxf). 2006;65(3):287–93.

[41] Taieb D, Timmers HJ, Hindie E, Guillet BA, Neumann HP, Walz MK, et al. EANM 2012 guidelines for radionuclide imaging of phaeochromocytoma and paraganglioma. Eur J Nucl Med Mol Imaging. 2012;39(12):1977–95.

[42] Baid SK, Lai EW, Wesley RA, Ling A, Timmers HJ, Adams KT, et al. Brief communication: radiographic contrast infusion and catecholamine release in patients with pheochromocytoma. Ann Intern Med. 2009;150(1):27–32.

[43] Furuta N, Kiyota H, Yoshigoe F, Hasegawa N, Ohishi Y. Diagnosis of pheochromocytoma using [123I]-compared with [131I]-metaiodobenzylguanidine scintigraphy. Int J Urol. 1999;6(3):119–24.

[44] Solanki KK, Bomanji J, Moyes J, Mather SJ, Trainer PJ, Britton KE. A pharmacological guide to medicines which interfere with the biodistribution of radiolabelled meta-iodobenzylguanidine (MIBG). Nucl Med Commun. 1992;13(7):513–21.

[45] Van Der Horst-Schrivers AN, Jager PL, Boezen HM, Schouten JP, Kema IP, Links TP. Iodine-123 metaiodobenzylguanidine scintigraphy in localising phaeochromocytomas—experience and meta-analysis. Anticancer Res. 2006;26(2B):1599–604.

[46] Fonte JS, Robles JF, Chen CC, Reynolds J, Whatley M, Ling A, et al. False-negative (1)(2)(3)I-MIBG SPECT is most commonly found in SDHB-related pheochromocytoma or paraganglioma with high frequency to develop metastatic disease. Endocr Relat Cancer. 2012;19(1):83–93.

[47] Kaji P, Carrasquillo JA, Linehan WM, Chen CC, Eisenhofer G, Pinto PA, et al. The role of 6-[18F]fluorodopamine positron emission tomography in the localization of adrenal pheochromocytoma associated with von Hippel-Lindau syndrome. Eur J Endocrinol. 2007;156(4):483–7.

[48] Vanderveen KA, Thompson SM, Callstrom MR, Young WF, Jr., Grant CS, Farley DR, et al. Biopsy of pheochromocytomas and paragangliomas: potential for disaster. Surgery. 2009;146(6):1158–66.

[49] Kimura N, Nakazato Y, Nagura H, Sasano N. Expression of intermediate filaments in neuroendocrine tumors. Arch Pathol Lab Med. 1990;114(5):506–10.

[50] Thompson LD. Pheochromocytoma of the adrenal gland scaled score (PASS) to separate benign from malignant neoplasms: a clinicopathologic and immunophenotypic study of 100 cases. Am J Surg Pathol. 2002;26(5):551–66.

[51] Strong VE, Kennedy T, Al-Ahmadie H, Tang L, Coleman J, Fong Y, et al. Prognostic indicators of malignancy in adrenal pheochromocytomas: clinical, histopathologic, and cell cycle/apoptosis gene expression analysis. Surgery. 2008;143(6):759–68.

[52] Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, Gimenez-Roqueplo AP, Grossman AB, et al. Pheochromocytoma: recommendations for clinical practice from the first international symposium. October 2005. Nat Clin Pract Endocrinol Metab. 2007;3(2):92–102.

[53] Pacak K. Preoperative management of the pheochromocytoma patient. J Clin Endocrinol Metab. 2007;92(11):4069–79.

[54] Mazza A, Armigliato M, Marzola MC, Schiavon L, Montemurro D, Vescovo G, et al. Anti-hypertensive treatment in pheochromocytoma and paraganglioma: current management and therapeutic features. Endocrine. 2014;45(3):469–78.

[55] Adler JT, Meyer-Rochow GY, Chen H, Benn DE, Robinson BG, Sippel RS, et al. Pheochromocytoma: current approaches and future directions. Oncologist. 2008;13(7): 779–93.

[56] Lenders JW, Eisenhofer G, Mannelli M, Pacak K. Phaeochromocytoma. Lancet. 2005; 366(9486):665–75.

[57] Gumbs AA, Gagner M. Laparoscopic adrenalectomy. Best Pract Res Clin Endocrinol Metab. 2006;20(3):483–99.

[58] Brauckhoff M, Thanh PN, Gimm O, Bar A, Brauckhoff K, Dralle H. Functional results after endoscopic subtotal cortical-sparing adrenalectomy. Surg Today. 2003;33(5):342–8.

[59] Pappachan JM, Raskauskiene D, Sriraman R, Edavalath M, Hanna FW. Diagnosis and management of pheochromocytoma: a practical guide to clinicians. Curr Hypertens Rep. 2014;16(7):442.

[60] Chino JP, Sampson JH, Tucci DL, Brizel DM, Kirkpatrick JP. Paraganglioma of the head and neck: long-term local control with radiotherapy. Am J Clin Oncol. 2009;32(3):304–7.

[61] Fishbein L, Bonner L, Torigian DA, Nathanson KL, Cohen DL, Pryma D, et al. External beam radiation therapy (EBRT) for patients with malignant pheochromocytoma and non-head and -neck paraganglioma: combination with 131I-MIBG. Horm Metab Res. 2012;44(5):405–10.

[62] Jimenez C, Rohren E, Habra MA, Rich T, Jimenez P, Ayala-Ramirez M, et al. Current and future treatments for malignant pheochromocytoma and sympathetic paraganglioma. Curr Oncol Rep. 2013;15(4):356–71.

[63] Ayala-Ramirez M, Feng L, Habra MA, Rich T, Dickson PV, Perrier N, et al. Clinical benefits of systemic chemotherapy for patients with metastatic pheochromocytomas or sympathetic extra-adrenal paragangliomas: insights from the largest single-institutional experience. Cancer. 2012;118(11):2804–12.

[64] Fishbein L. Pheochromocytoma and paraganglioma: genetics, diagnosis, and treatment. Hematol Oncol Clin North Am. 2016;30(1):135–50.

[65] Yuan R, Kay A, Berg WJ, Lebwohl D. Targeting tumorigenesis: development and use of mTOR inhibitors in cancer therapy. J Hematol Oncol. 2009;2:45.

[66] Boltze C, Mundschenk J, Unger N, Schneider-Stock R, Peters B, Mawrin C, et al. Expression profile of the telomeric complex discriminates between benign and malignant pheochromocytoma. J Clin Endocrinol Metab. 2003;88(9):4280–6.

[67] Druce MR, Kaltsas GA, Fraenkel M, Gross DJ, Grossman AB. Novel and evolving therapies in the treatment of malignant phaeochromocytoma: experience with the mTOR inhibitor everolimus (RAD001). Horm Metab Res. 2009;41(9):697–702.

[68] Zitzmann K, Ruden J, Brand S, Goke B, Lichtl J, Spottl G, et al. Compensatory activation of Akt in response to mTOR and Raf inhibitors—a rationale for dual-targeted therapy approaches in neuroendocrine tumor disease. Cancer Lett. 2010;295(1):100–9.

[69] Ayala-Ramirez M, Chougnet CN, Habra MA, Palmer JL, Leboulleux S, Cabanillas ME, et al. Treatment with sunitinib for patients with progressive metastatic pheochromocytomas and sympathetic paragangliomas. J Clin Endocrinol Metab. 2012;97(11):4040–50.