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Review article

Adrenal tumors

Advances in the management of pheochromocytoma – a short review

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Pheochromocytoma is a rare neuroendocrine neoplasm. It is characterized by overproduction of catecholamines, which causes clinical symptoms associated with elevated blood pressure values, and can even lead to life-threatening complications. The tumor can be associated with genetic syndromes such as multiple endocrine neoplasia type 2 (MEN-2) or von Hippel–Lindau syndrome (VHL), and currently available and constantly evolving genetic testing makes it possible to detect the inherited form and plan appropriate therapy. Management of pheochromocytoma is based on initial laboratory diagnosis, confirmation by imaging studies, determination of hormonal activity and resulting therapy. Surgical resection by laparoscopic approach is the most recommended. For unresectable tumors or advanced disease with distant metastases, systemic therapies under development currently allow the cure or inhibition of tumor progression. In this paper, we will review advances in management of pheochromocytoma over the past decade and potential directions for future research.

Key words: pheochromocytoma, management, imaging studies, systemic therapy, advances

Introduction

Pheochromocytoma is a rare neuroendocrine neoplasm occurring in an estimated average of 1 in 200,000 people. It is characterized by the overproduction of catecholamines originating from pathological chromaffin cells of the adrenal medulla. Only a small fraction metastasizes – approximately 10% of cases [1–4]. The classification of adrenal tumors in the group of endocrine tumors was updated by the WHO in 2017. The terms "benign" and "malignant" are currently no longer used for pheochromocytoma, as all of them (pheochromocytoma and paraganglioma – PPGL) present metastatic potential. To avoid confusion due to the former nomenclature, the WHO has replaced the term "malignant" with "metastatic" for pheochromocytoma. The terminology of paraganglioma also required systematization to distinguish between the histological origin and the anatomy of the lesion [5, 6]. Primary non-metastatic pheochromocytoma is most frequently associated with hereditary multiple endocrine neoplasia type 2A (MEN-2A). It is observed in 50% of MEN-2A patients, who have a somatic mutation of the *RET* gene. It also occurs in MEN-2B which is a much rarer syndrome [7–9]. The components of MEN-2 syndromes containing pheochromocytoma are summarized in table I.

Table I. Neoplasms and abnormalities included in MEN-2 [17]

MEN-2A (Sipple syndrome)	MEN-2B (Wagenmann-Froboese syndrome)
• medullary thyroid carcinoma • pheochromocytoma • primary hyperparathyroidism • normal physical appearance	• medullary thyroid carcinoma • pheochromocytoma • mucosal and gastrointestinal neuromas • marfanoid body habitus

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Currently, about 30-40% of all pheochromocytoma cases are considered to be hereditary. This neuroendocrine lesion must be differentiated from adrenocortical carcinoma, because it is approximately fifty times rarer and presents similar symptoms, but more often turns out to be metastatic [10, 11]. Due to its characteristics, a pheochromocytoma usually releases enormous amounts of catecholamines, metanephrines or methoxytramine that cause typical sympathetic nervous system manifestations. These could be headaches, tachycardia, hyperhidrosis or even episodic palpitations. They are also accompanied by other symptoms, mainly related to elevated blood pressure values. Less common symptoms include anxiety, panic attacks, seizures, abdominal pain, excessive sweating, diarrhea, nausea, polyuria, fever or weight loss. It is worth mentioning that some patients can be asymptomatic and tumors secreting different substances can provide different symptoms. For example, pheochromocytoma that secretes epinephrine may cause orthostatic hypertension, but a dopamine-secreting lesion would present normal blood pressure values [12, 13].

Untreated or inadequately treated pheochromocytoma can lead to a number of dangerous complications, including acute coronary syndrome, myocardial infarction, cardiogenic shock, Takotsubo-like and dilated cardiomyopathy. As can be seen, these are mainly cardiac related complications. Electrocardiographic changes mimicking myocardial ischemia like ST-elevations or T-wave depressions may also be observed in the course of pheochromocytoma. The tumor may also lead to life-threatening arrhythmias, visible in an ECG as prolongation of corrected QT interval or giant inverted T-waves [14]. However, pheochromocytoma, as a tumor secreting enormous amounts of catecholamines, may also cause hemorrhagic stroke, hypertensive crisis or spontaneous bleeding from the renal parenchyma (Wunderlich syndrome) as an extremely rare complication [15, 16]. The aim of this paper is to review the methods of diagnosis and therapy of pheochromocytoma and the progress that has been made over the past decade of research.

Review methods

For the preparation of this review paper, PubMed, PubMed Central and Google Scholar databases were searched. The phrases used for research were various forms and combinations of terms such as "pheochromocytoma", "pheochromocytoma diagnosis", "pheochromocytoma surgery", "pheochromocytoma systemic therapy", "pheochromocytoma genetics", "peptide receptor radionuclide therapy" or "tyrosine kinase inhibitors". Research was focused mainly on articles from the past decade to display developments and advances in the treatment. After reviewing the abstracts, articles that matched the aim of the work and focused on multidisciplinary diagnosis and therapy were selected. The analyzed papers were original articles, review articles and meta-analyses. Out of the articles from the initial research, 40 that comprehensively and adequately described the topic were selected. Finally, the obtained material was divided into groups of diagnosis, surgical treatment and systemic treatment of pheochromocytoma, and comprehensively described.

Diagnostics

Diagnosis of pheochromocytoma nowadays is based primarily on imaging examinations preceded by biochemical tests. Nowadays, thanks to advances in technology, the genes responsible for the formation of the tumor process have been discovered [18]. With suspicion of pheochromocytoma, either plasma-free metanephrines or fractionated urinary metanephrines are measured. Both methods appear to have a similar sensitivity and specificity. In the case of unclear results, a measurement of urinary dopamine, plasma 3-methoxytramine or even chromogranin A (CgA) can also be used. Following evident biochemistry results, imaging studies are performed starting with CT or MRI scans. Finally, methods such as PET-CT or ^{123}I-MIBG scintigraphy are used to confirm the hormonal activity of the tumor and plan the therapy [5].

Biochemical tests

Pheochromocytoma is a tumor that secretes catecholamines. Thus, it would seem logical to measure these compounds in plasma or urine. Previously it was the levels of catecholamines and their metabolites (vanillylmandelic acid, metanephrines, normetanephrines, 3-hydroxytyramine) in urine that were biochemically assessed by 24-hour urine collection. The current evidenced trend is the measurement of plasma-free metanephrines (metanephrine, normetanephrine, 3-MT), and it appears to be more reliable than the other types of tests, with 96.6% sensitivity and 94.9% specificity compared to the measurement of metanephrines in 24-hour urine collection (92.9% and 94.5%, respectively), but guidelines accept both tests for pheochromocytoma screening [19, 20]. Recent results reported that plasma-free metanephrines have a higher specificity than metanephines in 24-hour urine collection (95% *versus* 90%, respectively). A higher probability of pheochromocytoma is suggested by metabolite values exceeding more than twice the upper reference range. Elevated levels of a minimum of two metabolites also raise suspicion of a tumor. Biochemical testing should always be performed before imaging studies [19]. It has also been proven that the liquid chromatography-mass spectrometry (LC-MS) method has the highest testing accuracy and with liquid chromatography electron capture dissociation (LC-ECD), they are the gold standard nowadays that allows avoiding interactions with drugs. High performance liquid chromatography with electrochemical detection (HPLC-ECD) is considered more prone to analytical interference [19, 21]. However, there might be pitfalls in the diagnosis of PPGL. The possibility of false-positives should be remembered, so before measurements from both urine and plasma, the patient should

abstain from caffeine, tea, nicotine, alcohol, cheese or bananas, and discontinue medications such as MAO inhibitors, tricyclic antidepressants or SSRIs. When collecting the samples, it is important for the patient to remain fasting, without intense stress and in the supine position, which greatly increases the sensitivity of the test and reduces the cost of retesting [19, 22]. It has been proven that supine sampling has a higher testing sensitivity than seated sampling (95% to 89%, respectively) [23]. A case study published by Neary et al. shows that even in a patient with a family history of pheochromocytoma and a genetic burden, elevated levels of catecholamines do not automatically indicate a tumor. In a 51-year-old patient, an abnormal test result was caused by taking venlafaxine, a norepinephrine reuptake inhibitor that dramatically increased norepinephrine levels. In addition, α-adrenergic-receptor blockers and β-adrenergic-receptor blockers may reduce catecholamine-related symptoms and mask pheochromocytoma. Paracetamol may interfere with the aforementioned HPLC--ECD method and bias the test results. Thus, it is recommended to discontinue problematic drugs 24 hours before testing metanephrines in plasma or urine collection [24].

For non-functional pheochromocytomas, false-negative results may occur during standard measurements. The use of a CgA marker is helpful in such cases. This acid protein belongs to a group that forms the components of secretory granules of neuroendocrine cells. It shows 90% clinical sensitivity as an additive method to standard plasma-free metanephrine measurements, but the absence of its elevation cannot be used alone to exclude the presence of a tumor. However, it is also important to remember the possibility of CgA false results as in metanephrine tests. False-positive results may be caused by the treatment with proton pump inhibitors, histamine type-2 receptor antagonists, atrophic gastritis, impaired kidney function, inflammatory bowel disease, liver cirrhosis, hypercortisolemia, post-meal or post-exercise status. For this reason, it is recommended to rule out any medical disorders before the test, discontinue the aforementioned medications (at least 10 days for PPIs) and measure CgA after rest and fasting [25, 26].

Imaging techniques

Imaging uses traditional CT and MRI techniques, but diagnosis can be supplemented with scintigraphy using ^{123}I-MIBG (iodine-123-metaiodobenzylguanidine). Pheochromocytoma may be detected incidentally on routine imaging studies like CT or MRI on CT, pheochromocytoma is most often a solid, hypervascular and well-demarcated mass ranging in size from a few to 15 cm in its largest dimension. Larger tumors typically have a tendency for central necrosis. On MRI, tumors are hyperintense on T_2-weighted images and hypointense on T_1-weighted images. The advantages of ^{123}I-MIBG scintigraphy are the relatively low cost of the test, high image quality and low radiation exposure for the patient. The sensitivity of this method ranges from 83–100% and specificity from 95–100% in tumor detection. The method is very useful in planning radiotherapy with ^{131}I-MIBG [19]. Another method is imaging with PET-CT and ^{68}Ga-labeled DOTA peptides (DOTATATE, DOTATOC and DOTANOC). They are captured by somatostatin receptors (SSTRs) contained in each neuroendocrine tumor cell so that the location of lesions can be assessed with the greatest accuracy [27]. SSTR antagonists (^{111}In DOTA-BASS, ^{111}In-DOTA--JR11 or Ga-DOTA-JR11) are also used there. We can also use ^{18}F-fluorodopa in combination with PET-CT imaging. In this way we image L-type amino acid transporters. Data show that this technique has 100% sensitivity and is used in reputable centers to confirm an inconclusive result. A similar method is 18-fluorodeoxyglucose imaging using PET-CT [28–30].

Genetics and immunohistochemistry

According to a paper by Fishbein et al., the genes involved in the pheochromocytoma pathogenesis can be divided into three clusters, depending on their mechanism of action: pseudohypoxia, kinase signaling and Wnt signaling [31]. First cluster associated with pseudohypoxia and reduced oxidative response includes:

- *SDHx* – encoding succinate dehydrogenase complex,
- *vHL* – responsible for coding von Hippel–Lindau tumor suppressor, that is associated with pheochromocytoma, renal and pancreatic lesions,
- *DLST* – encoding the E2 subunit of mitochondrial α-ketoglutarate dehydrogenase,
- *SLC25A11* – determining the proper functioning of the malate-aspartate shuttle,
- *MDH2* – responsible for mitochondrial malate dehydrogenase that converts malate to oxaloacetate,
- *PHD1* – an unmutated gene activates HIF-1α and HIF-2α.

The second cluster, associated with abnormal activation of kinase-signaling pathways, includes:

- *PNMT* – expression is associated with the adrenergic phenotype of specific hereditary pheochromocytoma,
- *HRAS* – associated with increased expression of components of the RAS-MAPK signaling pathway and reduced expression of the DNA damage pathway.

The third cluster, connected with Wnt and Hedgehog signaling, includes genes like: *WNT4*, *DVL3*, *MAML3* and *CHGA*. The pathogenesis of pheochromocytoma also involves the genes *ATRX* and *H3F3A*. These genes are responsible for chromatin remodeling and H3.3 histone but are not classified into the aforementioned clusters. Genetic testing can be used after a diagnosis of pheochromocytoma to exclude an inherited form or to predict the prognosis and hormonal activity of the tumor. 65% of patients with a mutation of the aforementioned *SDHx* gene have high levels of catecholamines, and patients with second cluster gene mutations are more likely to develop epinephrine-producing tumors than norepinephrine-producing ones. Such tests appear to have numerous indications for

Table II. Overview of pheochromocytoma diagnostic methods

	Biochemical tests	Imaging techniques	Genetics and IHC methods
examples	• plasma-free catecholamines • urine catecholamines • plasma-free metanephrines • urine metanephrines • CgA	• abdominal CT • abdominal MRI • ^{123}I-MIBG scintigraphy • PET-CT with SSTR-binding DOTA peptides • ^{18}F-FDG PET-CT	• *SDHx*, *vHL*, *DLST* and other gene testing with molecular methods • IHC markers (CgA, synaptophysin) • *SDHx* mutations testing with IHC
notes	plasma-free metaephrines with LC-MS testing method have the highest accuracy, CgA is useful in non-functional pheochromocytoma, beware of false results (caused by drugs or diet)	should be performed after biochemical tests, routine tests as CT can detect the lesion, then nuclear medicine tests are performed allowing radionuclide treatment	mainly used after tumor diagnosis to determine heritability or metastatic potential; in prognosis prediction IHC as a more available method can be helpful in the diagnosis of genetic mutations

predicting prognosis, establishing a treatment plan or implementing preimplantation diagnosis.

Despite the utility of these tests, they are often expensive. For this purpose, the field of immunohistochemistry (IHC) is developing solutions to reduce costs and assess the pathogenicity of genetically uncertain tumors [19]. IHC methods were used to distinguish metastatic pheochromocytoma from a lesion without metastatic potential, because of the difficulty of doing this in histological methods. It was proven that of the tested IHC markers (e.g., CgA, synaptophysin, S-100, Ki-67, melan-A, inhibin), the first two show utility in predicting the neuroendocrine nature of the tumor. Their immunoreactivity was presented as granular cytoplasmic staining with variation in the intensity in different tumor areas. Overall intensity was higher for chromogranin than for synaptophysin. High variability in the architectural patterns of tumor cells in each lesion prevented the effective use of S-100. High levels of Ki-67 proved specific, but insufficient to predict the metastatic potential of pheochromocytoma independently. Melan-A and inhibin did not show immunoreactivity. The study proved that IHC with the use of these markers is not helpful in predicting the clinical behavior of pheochromocytoma but only in confirming the neuroendocrine nature of the examined lesion [32].

Currently, IHC is collaborating with previously described genetic methods in the diagnosis of mutations in patients with pheochromocytoma. It mainly investigates mutation of the *SDHx* gene through loss of expression of SDHA, SDHB, SDHC and SDHD proteins. The sensitivity and specificity of SDHB IHC in the *SDHx* subunit mutation are 95.0% and 81.8%, respectively. Interobserver variation using SDHB/SDHA immunohistochemistry when there is a poor diffuse SDHB interpretation is also being investigated [30]. In a recent study, Su et al. found that patients with SDHB(–) had a significantly worse prognosis and shorter survival time than patients with SDHB(+). The authors emphasize the possible benefits of these findings, as it is possible to predict the prognosis of mutation-laden pheochromocytoma patients on the basis of these results and include them in a more rigorous follow-up.

Without IHC, this would not be possible on a larger scale, due to the cost and low availability of genetic testing. The IHC procedure can be successfully performed in most centers. There is certainly a need for larger clinical trials in this area, however at present, the use of IHC in pheochromocytoma genetics appears to be a future avenue [33]. Information on the diagnosis of pheochromocytoma is summarized in table II.

Therapy

Over the years, pheochromocytoma therapy has been based on several essential principles: surgery, chemotherapy and radiotherapy. Recently, due to the rapid development of molecular biology, we can also include individualized immune agents in the treatment [34, 35]. The choice of the therapy should include factors such as the resectability of the tumor, its infiltration of adjacent structures, the presence of distant metastases, the amount of hormones secreted by the tumor, its growth rate and the patient's comorbidities. The principal treatment of a pheochromocytoma secreting significant amounts of hormones is surgical resection with perioperative adrenergic receptor blockade, as it is necessary to improve the patient's condition as quickly as possible and prevent severe cardiovascular complications. The presence of disseminated inoperable malignancy disqualifies from surgical treatment. In order to improve the patient's condition, slowing tumor progression and reducing the amount of hormone secretion, systemic treatments such as radiation therapy, chemotherapy or pharmacotherapy are used. Unlike in the case of hormonally active or metastatic lesions, for tumors indolent in hormone secretion or non-metastatic, the "watch and wait" strategy is currently accepted [19].

Surgical treatment

Surgical treatment seems to be associated with a relatively low 5-year survival rate (45%). This is justified by the location of the tumor itself, as well as the difficulty of resecting metastases and the formation of postoperative complications. The preferred method is laparoscopy due to the lower invasiveness of the procedure, but the presence and nature of metastatic lesions most often require modification of the procedure to laparotomy. It was indicated that the limiting tumor size for laparoscopic surgery is 6 cm [18, 36, 37].

A different survival rate was reported by De Filpo et al. which described currently surgical resection of a metastasis--free tumor using available imaging technologies at the time of initial advancement results in a 5-year survival rate of more than 90% [38]. In addition, Amar et al. suggest that it is possible to achieve a decreased rate of postoperative complications of pheochromocytoma with a complete and thorough resection [39]. At this point, it is worth mentioning the anesthesia procedure during pheochromocytoma resection, considered one of the most difficult challenges in anesthesiology practice. Procedures such as laryngoscopy, endotracheal intubation or the manipulation of the tumor itself, could be the triggers that cause catecholamine spikes and hemodynamic instability. The standard procedure is to administer a long-acting benzodiazepine (e.g. diazepam) the night before surgery and α-blockade with shorter-acting drugs (e.g. prazosin) or longer-acting drugs (e.g. phenoxybenzamine); however, drugs with longer half-lives should be withheld 12–24 h before surgery. H_2-blockers are also useful. Propofol or etomidate are used for anesthesia induction but ketamine is not recommended due to its sympathicomimetic effects. The key problem of anesthesia induction appears to be the pressor response to laryngoscopy and endotracheal intubation. Agents like fentanyl, lidocaine, esmolol, nitroglycerin or nicardipine are useful in this case. A recommended depolarizing agent is vecuronium, due to its lack of histamine release, unlike pancuronium. The inhalation anesthetics used are most commonly sevoflurane, enflurane and isoflurane, and opiates are long-acting agents (morphine, hydromorphone) [40, 41].

Systemic treatment

Treatment with somatostatin analogs like Yttrium-90-DOTATOC (^{90}Y-DOTATOC) and lutetium-177-DOTA0-Tyr3-octreotate (^{177}Lu-DOTATATE) has become one of the radiotherapeutic approaches. Lowery A. et al. described a phase II clinical trial for the treatment of pheochromocytoma with an already known radionuclide ^{131}I-MIBG, but at a higher dose. Such a therapy yielded a 5-year survival rate of 64%. On the other hand, the use of somatostatin analogs ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE in a group of patients led to at least partial remission in 46% of the subjects [42]. Another treatment method is the use of chemotherapeutics, especially in patients refractory to radiotherapy. A CVD regimen, consisting of cyclophosphamide, vincristine and dacarbazine, was widely used. It provided an average of 5.5 months without recurrence of the neoplastic process. It was also indicated that a better prognosis was provided by the association of CVD with anthracyclines and oral temozolomide. Biological drugs were gradually introduced into treatment as new substances that yielded promising results in therapy. The known molecular pathway responsible for the pathogenesis of pheochromocytoma has allowed the use of inhibitors of its individual substrates. The mTOR inhibitor everolimus was used in therapy with apparent improvement, albeit unfortunately short lived. Sunitinib, a tyrosine kinase inhibitor (TKI), found therapeutic use, while another drug with the same effect, imatinib, did not provide such promising results [43–48].

Zhang et al. published a pheochromocytoma treating method with a novel immune therapy – a combination of the mTORC1 and mTORC2 inhibitor drug called PP242. The study was conducted on mice. The previously known drug rapamycin, an mTOR1 inhibitor, was compared with the newly discovered substance. Clinical studies showed that PP242 significantly inhibited tumor growth due to the molecular inhibition of the activation of the effector protein in the mTOR pathway and caused activation of apoptosis in tumor cells [49]. Antonio K. et al. described a chemotherapeutic BEZ235. Its antitumor effect is based on several important choke-points. It inhibits phosphoinositide 3-kinase (PI3K), the mTOR1 and mTOR2 complexes. Molecularly, there is a decrease in the expression of the norepinephrine transporter by inducing cytotoxic and antiproliferative effects. The result is the induction of cell apoptosis with a significant reduction in proliferation and angiogenesis [30]. Research has also been conducted on the heat shock protein Hsp90.

Giubellino et al. attempted to cure pheochromocytoma by targeting this protein. The experiment was conducted *in vitro* on a human cell line and *in vivo* on mice. Tested cells were infected with human pheochromocytoma cells. After that, the experimental substances were applied: 17-AAG (17-allylamino-17-demethoxygeldanamycin) and ganetespib, a second-generation Hsp90 inhibitor. In both parts of the experiment, apoptosis of certain tumor cells and a definite reduction in the ability to form metastases were observed, with ganetespib showing a stronger effect at a given concentration [50].

Another treatment strategy was tested by Zhang et al. on mice. The therapy was a combination of both mTORC2 and Hsp90 inhibition. The use of only one agent inhibited the proliferation in the majority of cells, but the additive action of both agents resulted in an increased effect. Apoptosis of tumor cells and their metastatic migration occurred in the same manner [51].

Based on previous experience, Mercado-Asis et al. clearly indicated that the future of treatment will be the association of biological drugs with each other. Single-component formulations do not provide sufficient efficacy, since inhibition of a selected pathway results in the upregulation of a collateral pathway. A small-molecule HIF-2α inhibitor was being investigated. It was molecularly designed to block unrestrained tumor cell growth and proliferation, tumor angiogenesis and the suppression of antitumor immune responses. Also at the clinical trial stage at the time was a topoisomerase I inhibitor, thought to reduce tumor growth and metastatic potential [28, 29].

Targeted therapies were also analyzed by Corssmit et al. The substances were: axitinib and pazopanib, a drug from

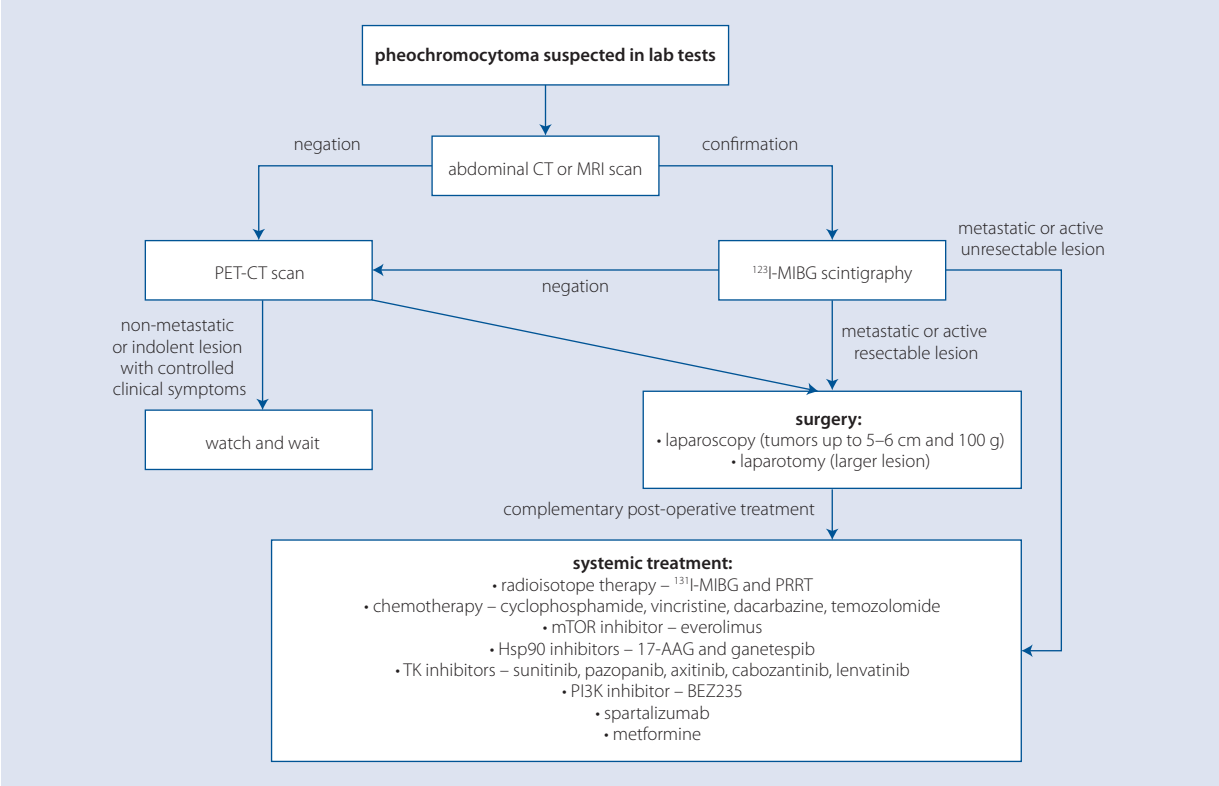

Figure 1. Management algorithm for patients with pheochromocytoma

the long-known group of antiangiogenic receptor TK inhibitors. The initial phases of the study did not show spectacular benefits from their use. In the initial stages of experiments there are two more substances, lenvatinib and cabozantinib. A poly(ADP-ribose) polymerase inhibitor that is responsible for chemotherapy resistance was also discovered. Its inhibitor, olaparib, is showing promising therapeutic activity. A group of immunomodulatory drugs that are also in clinical trials – nivolumab, ipilimumab and pembrolizumab – have also been stopped. These substances are checkpoint inhibitors, allowing for the process of apoptosis to be irreversibly inhibited in neoplastic cells [52, 53]. Spartalizumab, a humanized monoclonal antibody capable of binding to the programmed death checkpoint protein receptor, is also in clinical trials [38].

One of the most recent experimental therapies was described by Meireles et al. and involves the administration of metformin. The study was conducted on rat and human cell lines. The results showed that this substance inhibited PC12-ADH cell proliferation and reduced oxygen consumption, ATP production and proton leakage, as well as loss of mitochondrial membrane potential. In addition, metformin induced AMPK phosphorylation and impaired activation of the AMPK-PI3k-AKT-mTOR pathway [54].

The latest treatment direction for pheochromocytoma was published by Tabebi et al. The target point of the therapy is suggested to be striking the nuclear and mitochondrial genetic material of the neoplasm cells. At the stage of early clinical trials, there are substances that are intended to achieve this goal and represent an optimistic view of the future in pheochromocytoma therapy [55]. The management of patients with pheochromocytoma is reviewed in figure 1.

Conclusions

Pheochromocytoma is a rare neuroendocrine tumor that represents a major therapeutic challenge. Its diagnosis is based on both laboratory and imaging studies, which are being supplemented all the time with new possibilities using the resources of nuclear medicine. Still, the largest number of these tumors are detected incidentally before the onset of alarming clinical symptoms. The great advances that have been made over the past decade now make it possible to detect tumors at an earlier stage, and the gene clusters and carcinogenesis pathways that are being discovered make it possible to predict prognosis and plan the treatment. Surgical resection of the tumor is still the therapy of choice, but when it is not an option, currently existing and developing systemic therapies are able to inhibit or slow tumor growth and limit clinical symptoms. The large range of chemotherapeutics in clinical trials offers hope for the future in pheochromocytoma therapy.

Article information and declarations

Author contributions

Michał Miciak – conceptualization, methodology, writing, review and editing of the manuscript.

Krzysztof Jurkiewicz – conceptualization, methodology, writing, review and editing of the manuscript.
Krzysztof Kaliszewski – conceptualization, methodology, review and editing of the manuscript, supervision.

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Conflict of interest

None declared

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