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SARCOMAS (SR PATEL, SECTION EDITOR)

Treatment for Malignant Pheochromocytomas and Paragangliomas: 5 Years of Progress

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Abstract
Purpose of Review The purpose of this manuscript is to review the progress in the field of therapeutics for malignant pheochromocytomas and sympathetic paraganglioma (MPPG) over the past 5 years.
Recent Findings The manuscript will describe the clinical predictors of survivorship and their influence on the first TNM staging classification for pheochromocytomas and sympathetic paragangliomas, the treatment of hormonal complications, and the rationale that supports the resection of the primary tumor and metastases in patients with otherwise incurable disease. Therapeutic options for patients with bone metastasis to the spine will be presented. The manuscript will also review chemotherapy and propose a maintenance regimen with dacarbazine for patients initially treated with cyclophosphamide, vincristine, and dacarbazine. Finally, the manuscript will review preliminary results of several phase 2 clinical trials of novel radiopharmaceutical agents and tyrosine kinase inhibitors.
Summary MPPGs are very rare neuroendocrine tumors. MPPGs are usually characterized by a large tumor burden, excessive secretion of catecholamines, and decreased overall survival. Recent discoveries have enhanced our knowledge of the pathogenesis and phenotypes of MPPG. This knowledge is leading to a better understanding of the indications and limitations of the currently available localized and systemic therapies as well as the development of phase 2 clinical trials for novel medications.

Keywords Malignant pheochromocytoma · Malignant paraganglioma · Surgery · Bone metastases · Chemotherapy · Clinical trials

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Introduction

Pheochromocytomas and sympathetic paragangliomas (PPGs) are neuroendocrine tumors originating in the paraganglia. These tumors are frequently characterized by an excessive secretion of catecholamines that predispose patients to symptoms such as hypertension, palpitations, throbbing headaches, and sweats. Because symptoms are not specific, the diagnosis of these tumors is frequently missed. Biochemical studies with high sensitivity such as the measurement of plasma-free metanephrines or 24-h urine collection for fractionated metanephrines rule out PPG in the vast majority of patients [1]. Conventional imaging (computed tomography/magnetic resonance) localizes PPGs, with high sensitivity rates [2]. Functional imaging studies may complement conventional imaging studies in patients with particular characteristics (i.e., pheochromocytomas larger than 5 cm, a noradrenaline phenotype, hereditary predisposition, or metastatic disease) [2, 3]. Germline gene testing is recommended to every patient with PPG [3].

Although there has been substantial progress in characterizing the clinical, biochemical, imaging, and genotypic

features of these tumors, the treatment of malignancy is a persistent challenge. Approximately 15–17% of PPGs are malignant (MPPGs) [4]. Currently, a PPG is considered malignant only when metastasis is present; no histologic or molecular marker can clearly differentiate benign PPG from MPPG. When metastasis is detected, the disease is usually advanced and the prognosis is poor, with a median 5-year overall survival (OS) rate of only 60% [5].

For the past several decades and in most countries, therapeutic options for MPPG have been limited to chemotherapy and iodine^{131} (^{131}I) meta-iodo-benzylguanidine (MIBG). Our knowledge of these treatments relies on the results of a few mainly retrospective studies. Up to 70% of MPPGs apparently do not respond to these treatments [6, 7]. No official guidelines on the treatment of MPPG exist. Nevertheless, over the past decade, clinical characterization and understanding of the genetic and molecular causes of MPPG have substantially improved [8]. Recent studies have recognized the value of surgical resection of the primary tumor in patients with no curable disease, and new systemic therapies have emerged [9•, 10]. The purpose of this manuscript is to provide an update on the progress of localized and systemic therapies for MPPG.

Predictors of Survival

Unlike in many other malignancies, the natural history of MPPG is heterogeneous, as indicated by the OS and progression-free survival (PFS) curves, and consequently, clinical outcomes of patients with MPPG are difficult to predict [5, 11]. Some patients have indolent disease; these patients may have extensive distant metastases that do not change over time, and consequently, these patients may be alive and have excellent quality of life several years after the initial diagnosis. These patients frequently need minimal or no therapeutic intervention. Conversely, some patients exhibit very aggressive disease characterized by fast replication, massive metastases, and no response to systemic therapy. These patients have very short OS durations. However, most patients exhibit intermediate outcomes with progressive disease that will require intervention at some point [11].

Several factors predict survival, including the size and location of the primary tumor; germline *SDHB* mutations; size, location, and timing of metastases; and complications due to excessive catecholamines.

Primary Tumor Size and Location

Several studies have demonstrated that a large primary tumor is associated with a high rate of metastasis [4, 12–14]. These studies have described size cutoffs ranging from 4 to 6 cm as predictors of distant spread. However, most of these studies are small and lack multivariable analysis. The largest study on clinical predictors of malignancy, and the only one with multivariable analysis of OS, noted that patients with PPGs bigger than 5 cm had a high rate of metastasis and decreased OS [4]. Only 3% of pheochromocytomas smaller than 5 cm resulted in distant metastasis. The location of the primary tumor was a predictor of metastasis and OS [4]. Up to 70% of patients with sympathetic paragangliomas had distant metastasis [4], and 20% of these patients had primary tumors smaller than 5 cm [4]. A multivariable analysis confirmed that the primary tumor location was a more powerful predictor of metastasis and OS than the primary tumor size [4]. The TNM staging for patients with PPG has adopted a cutoff of 5 cm and the extra-adrenal location as important determinants of risk of metastasis and OS [15•] (Table 1).

Approximately 50% of patients with MPPG present with metachronous metastases, which are defined as new sites of tumor development occurring years or decades after initial diagnosis of the primary tumor [4]. Thus, patients with clinical predictors of malignancy need long-term follow-up [4–6].

Molecular Predictors of Survival

The most important molecular predictor of malignancy is the presence of inactivating germline mutations of the subunit B of the mitochondrial enzymatic complex 2 or succinate dehydrogenase (*SDHB*). These mutations also predispose patients to rare kidney cancers and gastrointestinal stromal tumors. Approximately 50% of patients with *SDHB*-PPG present with metastasis and have poor OS durations; this is a striking difference when compared with patients with mutations in other subunits of the succinate dehydrogenase. The *SDHB* mutation results in a hypermethylation phenotype with abnormal activation of epithelial-to-mesenchymal transition, which might explain why this is a more aggressive phenotype [16, 17]. Amar et al. compared the phenotypes of *SDHB*-MPPG and apparently sporadic MPPG and found that patients with *SDHB*-MPPG had significantly shorter OS durations [18]. Ayala-Ramirez et al. found that the OS rates of patients with metastatic pheochromocytomas was similar to that of patients with metastatic sympathetic paragangliomas [4]; this is an interesting finding given that the *SDHB* phenotype is mainly characterized by extra-adrenal tumors. Patients with very aggressive apparently sporadic MPPG have also been described. Thus, whether *SDHB*-MPPGs are indeed more aggressive than other apparently sporadic tumors needs to be confirmed by larger, comparative, and prospective studies.

Germline mutations of the fumarate hydratase gene, somatic mutations of *NF1* and *ATRX*, and fusions of mastermind-like transcriptional coactivator 3 are also associated with malignancy [19–21]. The impact of these mutations on long-term OS needs to be determined. Malignancy has rarely been described in carriers of germline mutations of the *RET*, *MAX*,

Table 1 TNM classification of malignant pheochromocytoma and paraganglioma

Primary tumor size	
TX	Primary tumor cannot be assessed
T1	Tumor < 5 cm in greatest dimension, no extra-adrenal invasion
T2	Tumor ≥ 5 cm or sympathetic paraganglioma of any size, no extra-adrenal invasion
T3	Tumor of any size with invasion into surrounding tissues (e.g., liver, pancreas, spleen, kidneys)
Regional lymph nodes	
NX	Regional lymph nodes cannot be assessed
NO	No lymph node metastasis
N1	Regional lymph node metastasis
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis
	M1a: Distant metastasis to only bone
	M1b: Distant metastasis to only distant lymph nodes/liver or lung
	M1c: Distant metastasis to bone plus multiple other sites

TMEM127, and *NF1* genes [22–24]. Tumors associated with activating mutations of the *RET* proto-oncogene (multiple endocrine neoplasia type 2) are rarely malignant even though the primary tumor is often large [22]. *RET* mutations do not predispose patients to PG [22].

Metastasis as a Predictor of Survival

Distant metastases of MPPG mainly occur in the lymph nodes (80%), skeleton (72%), liver (50%), and lungs (50%) [5]. Local infiltration of the liver, pancreas, kidneys, gastrointestinal tract, and adipose tissue may also occur. Metastases to the brain, breasts, skin, and ovaries have rarely been described. As in other cancers, patients with large tumors and synchronous metastasis exhibit a poor prognosis [9]. The location of metastasis is a determinant factor of prognosis. Twenty percent of patients may present with only bone metastasis [25]. These patients exhibit longer OS compared with patients with liver and/or lung metastases [25]. The aggressiveness of bone metastasis, however, should not be underestimated. Patients with bone metastasis are prone to skeletal-related events, which can result in morbidity and mortality [25].

Catecholamine Excess

Most MPPGs secrete catecholamines such as adrenaline, noradrenaline, and dopamine. Dopamine excess typically does not cause endocrine manifestations, but adrenaline and noradrenaline excess may predispose patients to various types of cardiovascular, metabolic, and gastrointestinal diseases. Deaths have been described because of hypertension complicated with strokes, heart attacks, arrhythmias, congestive heart failure, and pulmonary edema, as well as diabetes mellitus decompensation and severe constipation [6]. However, tumor burden is a more important predictor of OS and most deaths are caused by MPPG progression [9].

Treatment

The goals of treatment are to reduce tumor size, treat catecholamine-related adverse events, palliate symptoms related to tumor burden, and prevent tumor progression.

Treatment of Hormonal Complications

Catecholamine secretion is directly proportional to tumor burden; thus, manifestations of hormone excess can be severe. Anesthesia and tumor manipulation during surgery and tumor destruction due to chemotherapy, radiopharmaceutical agents, or tyrosine kinase inhibitors may predispose patients to a hypertensive crisis and cardiovascular events. All patients with hormonally active MPPG must be treated with alpha- and beta-blockers. Free salt and liquid intake is encouraged to promote intravascular expansion [6]. Calcium channel blockers, angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and other vasodilators (e.g., hydralazine) are frequently added because hypertension may be difficult to control [26]. Furthermore, these medications may prevent the use of high doses of alpha- and beta-blockers and the resulting adverse effects [26].

MPPGs that predominantly secrete noradrenaline may decrease gastrointestinal motility, leading to constipation. This symptom is frequently ignored and may worsen over time, predisposing patients to pseudo-obstruction, intestinal ischemia, perforation, and sepsis [27]. A high-fiber diet, adequate liquid intake, and stool softeners such as docusate and senna correct mild to moderate constipation and prevent progression to severe, sometimes lethal constipation [27]. Treatment for

severe constipation must be systematic [27]. Of note, alpha- and beta-blockers do not treat constipation because these medications cannot reactivate gastrointestinal motility [27].

Surgery

Surgical resection of the primary tumor in patients with otherwise not curable disease could have a very positive impact on clinical outcomes [9]. Resection of the primary tumor causes a reduction of the catecholamine surge improving cardiovascular and gastrointestinal manifestations and may prevent anatomical complications (i.e., urinary tract obstruction) [9]. Of most importance, the resection of the primary tumor is associated with improvements of OS [9]. This improvement is likely related to a decreased rate of distant metastases.

Local recurrences and regional malignant lymphadenopaties are common [9]. Subsequently, the preferable surgical approach for patients with metastatic disease or clinical predictors of malignancy should be an open laparotomy; a regional lymphadenectomy should also be considered. Preoperative MIBG and FDG-PET scans may complement CT/MRI when trying to determine the regional extension of the disease [28]. In anticipation for surgery, patients must have adequate preparation with alpha- and beta-blockage and acceptable performance status [9, 26]. Surgery is complex and requires of an experienced team.

Chemotherapy

Since the late 1960s, various chemotherapeutics have been described as potential treatments for MPPG [29]. These drugs include cyclophosphamide, doxorubicin, vincristine, dacarbazine, temozolomide, 5-fluorouracil, methotrexate, ifosfamide, streptozotocin, and platinum compounds. The drugs inhibit different phases of the cellular cycle, leading to cancer cell death, and they are effective for the treatment of many malignancies. Alone or in combination, these drugs have been difficult to study in patients with MPPG given the rarity of the disease, and consequently, the drugs are not approved by the US Food and Drug Administration to treat MPPG. Nevertheless, these drugs have been used internationally for several years because they are frequently the only systemic therapies available.

All published studies on chemotherapy are retrospective in nature and typically include small cohorts of patients with heterogeneous or poorly defined tumor characteristics. Most of these studies also lack characterization of tumor prognostic factors such as tumor burden, location and size of the primary tumor, *SDHB* mutations, timing of metastasis, and progression prior to chemotherapy. The best studied protocol combines cyclophosphamide, vincristine, and dacarbazine (CVD) [29].

A meta-analyses of the largest studies on CVD showed that only 37% of patients exhibited a radiographic response [30]. Moreover, this rate could be an overestimation because most studies likely included some patients with minimal or no disease progression. It is not surprising that the rates of response are low and complete responses are exceptional because most patients present with advanced large tumor burden at diagnosis (TNM stage 4) [31]. Ayala-Ramirez et al. reported a 5-year OS rate of 51% among patients with MPPG who received CVD [31]. Patients in that study were classified as responders or nonresponders depending on how much the tumor shrank according to conventional radiography results and how well blood pressure was controlled (as determined by dose reductions and the number of antihypertensive medications used). All patients had disease progression prior to chemotherapy and 33% had radiographic and clinical evidence of response to CVD. Responders had a median OS of 6.4 years compared with 3.7 years in nonresponders, but this difference was not statistically significant ($p = 0.095$). However, in a multivariable analysis adjusting for tumor size at the time of diagnosis, median OS was significantly longer among those who received CVD ($p = 0.05$; hazard ratio = 0.22; 95% confidence interval = 0.05–1.0). Ayala-Ramirez's study is the only one to suggest that CVD offers a survival benefit. However, the study did not show that clinical prognostic indicators were good predictors of a therapeutic response to CVD [31].

Other chemotherapy regimens consisting of agents such as cisplatin, 5-fluorouracil, methotrexate, ifosfamide, and streptozotocin have also been used to treat MPPG, but the evidence to support their prescription is not strong [32]. Consequently, it is not possible to determine which chemotherapy combination is the best in terms of PFS, OS, and quality of life.

A recent study attempted to describe the natural history of MPPG in treatment-naïve patients [11]. Approximately 50% of patients had disease characterized by minimal or no progression at 1 year after initial diagnosis. Frequently, the tumor burden in these patients was asymptomatic and symptoms of catecholamine excess were easily treated with alpha- and beta-blockers and other supportive therapies [11]. As such, these patients were not considered candidates for CVD because this protocol is not expected to cure the disease and may alter the patient's quality of life, especially with cumulative doses [5, 6]. Patients likely to benefit from chemotherapy are those who have rapidly growing tumors that exhibit radiographic progression over a short period of time (< 6 months), manifestations of disease progression (e.g., skeletal-related events, malignant pleural effusions, compression of adjacent organs), and/or overwhelming symptoms of catecholamine excess that cannot be easily controlled by supportive therapies [5, 26].

Some oncologists have recommended the long-term use of CVD for tumor control and prevention of resistance. However, the side effects of CVD are not negligible and may negatively impact the patient's quality of life. Vincristine may cause peripheral sensorial and autonomic neuropathy with disability and overwhelming constipation

[33, 34]. Rare cases of leukemia and myelodysplastic syndrome have been reported [31]. A recent study of 15 patients treated with temozolomide alone suggested that this treatment may have a positive impact on patients with *SDHB*-MPPG [35]. However, this observation was not confirmed by Ayala-Ramirez et al. [31], although they suggested that some patients may be treated with temozolomide/dacarbazine alone [35]. Thus, in patients who initially respond to CVD (i.e., at least a partial radiographic response or disease stabilization and clinical improvement), a maintenance regimen with dacarbazine or temozolomide alone could be implemented after six to nine cycles of CVD. This maintenance regimen, which is similar to that used in patients with colon, lung, and ovarian cancers [36–38], could help reduce side effects and provide an acceptable quality of life, and PFS rates may also be improved. Given the lack of therapeutic options, this approach would allow patients to resume first-line medications that had been discontinued, thereby preventing or delaying the use of second-line therapies.

There is currently no evidence to support the use of adjuvant chemotherapy in MPPG. It is not clear whether treatment with four to six cycles of CVD after surgery in patients with predictors of malignancy could decrease the risk for local or distant disease recurrence or progression or improve PFS and OS. This should be investigated in a randomized phase 3 clinical trial.

In most cancers, the goals of neoadjuvant chemotherapy are to obtain a partial response in patients with locally advanced disease so that surgical resection is feasible, to achieve a complete pathologic response to improve prognosis and survivorship, and to preserve the organ of origin. Because most patients with MPPG are diagnosed with advanced disease, the role of neoadjuvant chemotherapy in the treatment of MPPG has not been determined.

Radiopharmaceutical Treatments: ^{131}I-MIBG and ^{131}I-Ultratrace Iobenguane

MIBG is a norepinephrine analogue that is taken up by cells in the sympathomedullary system, acting as a semi-selective agent for MPPG. MIBG can be utilized for both diagnostic and therapeutic purposes by labeling with radioisotopes of iodine. When formulated with ^{131}I, MIBG can be used to treat MPPG metastases if the lesions demonstrate uptake on pretherapy MIBG imaging. ^{131}I-MIBG has been shown to achieve therapeutic effect (i.e., response according to biochemical and imaging criteria) when the beta-minus decay of ^{131}I causes radiation damage to the target tissue [39].

Both ^{123}I-MIBG and ^{131}I-MIBG can be used for imaging purposes to evaluate the avidity and extent of metastatic lesions [40]. Two-dimensional whole-body planar imaging can be performed following the intravenous administration of ^{123}I-MIBG or ^{131}I-MIBG. Single-photon emission computed tomography imaging can also be performed, providing a three-dimensional distribution of activity. Single-photon emission computed tomography images can be combined with computed tomography images to provide anatomical detail and aid in the localization of foci of MPPG. ^{123}I-MIBG is typically preferred to ^{131}I-MIGB for imaging because ^{123}I lacks beta emissions and has a shorter half-life (13.2 h compared with 8 days), resulting in overall lower radiation exposure for the patient. In addition, compared with ^{131}I, the gamma emission of ^{123}I is more optimal for imaging with conventional gamma cameras given the lower-energy photons. The longer half-life of ^{131}I-MIBG is preferable to ^{123}I-MIBG when dosimetry is desired because images can be obtained at multiple time points over several days, which can aid in the estimation of radiation absorbed dose to specific organs.

^{131}I-MIBG therapy has been evaluated in a number of relatively small clinical trials but is not currently approved by the US Food and Drug Administration for MPPG. Approaches in clinical trials have differed in terms of the amount of activity administered per treatment cycle, the total number of treatments, and treatment intervals. Although regimens have varied substantially, they can be categorized into two basic strategies: multiple relatively low-dose treatments or a limited number of high-dose treatments. Both high-dose regimens and fractionated low-dose regimens have been shown to be effective in achieving a therapeutic response [41].

A meta-analysis of 17 studies published between 1984 and 2012 included 243 patients with MPPG treated with ^{131}I-MIBG, and follow-up durations ranged from 24 to 62 months. Patients received a wide range of both the number of treatments and cumulative activity. The median cumulative activity administered ranged from 186 to 1065 mCi (6882–39,400 MBq) and the median number of infusions ranged from one to seven. A complete response was observed in 3% of patients, a partial response in 27% of patients, and stable disease in 52% of patients. Biochemical responses were as follows: 11% complete response, 40% partial response, and 21% stable disease [7]. Patients whose disease is limited to soft tissue involvement have been reported to achieve better objective responses to ^{131}I-MIBG therapy than patients with bone metastases [42].

At relatively low doses, ^{131}I-MIBG is generally well tolerated. The most common adverse effects are anorexia, nausea, vomiting, mild leukopenia, and thrombocytopenia [43]. Among patients who have undergone high-dose therapy, sustained complete response has been reported in a small number of patients but the risk of potentially serious adverse effects was increased. In one study of 12 patients who received high doses, with a median cumulative activity of 1015 mCi (37,555 MBq), three patients achieved complete response, and two of these patients had soft tissue and skeletal metastases. Partial response was achieved in seven patients, and two patients died with progressive disease. Grade 3

thrombocytopenia occurred following 79% of treatments. Grade 3 neutropenia occurred following 53% of treatments and grade 4 neutropenia occurred following 19% [44]. Acute myeloid leukemia and myelodysplastic syndrome have also been reported after multiple infusions of high-dose ^{131}I-MIBG [45].

Ultratrace iobenguane ^{131}I is a promising form of ^{131}I-MIBG with high specific activity. In Ultratrace iobenguane ^{131}I, a labeling approach is used, resulting in radiolabeled MIBG without the addition of a carrier. Uptake by the norepinephrine transporter is a competitive process, and therefore, the presence of cold (non-radiolabeled) MIBG can diminish the uptake of radiolabeled ^{131}I-MIBG within target tissue. The bioactive carrier molecule does not contribute to the therapeutic response but can contribute to adverse effects such as hypertension, nausea, and vomiting when administered in high doses. In animal models, ^{131}I-MIBG with high specific activity has been shown to result in higher levels of radioactivity in the target tissue, greater therapeutic efficacy, and less appreciable cardiovascular side effects compared with the carrier-added counterpart [46]. Ultratrace iobenguane ^{131}I has been used safely in humans [47] and is under evaluation as part of a phase 2 clinical trial designed to evaluate its effectiveness in patients with MPPG. The primary outcome measure in this trial is reduction in antihypertensive medications, and the secondary measures are overall tumor response, OS, quality of life, and safety [48•]. Preliminary results from 44 patients are impressive. At 12 months, 35% of patients experienced sustained blood pressure control and 93% had a positive objective response. Four patients had severe but reversible thrombocytopenia. At the time the current manuscript was written, the trial had completed recruitment (n = 75).

Tyrosine Kinase Inhibitors

Several multi-tyrosine kinase inhibitors are under evaluation for the treatment of MPPG [10]. These medications include sunitinib, cabozantinib, axitinib, pazopanib, and lenvatinib. All of these medications inhibit angiogenesis; some may inhibit unique receptors that modulate tumor growth and spread. Cabozantinib is a c-met inhibitor [49] and lenvatinib blocks the fibroblast growth factor receptor [50].

The most compelling published information to date on tyrosine kinase inhibitors relates to an intention-to-treat retrospective study of patients with progressive MPPG treated with sunitinib [51]. This study included 17 patients, of which 47% showed clinical and radiographic benefits from the treatment. Given the retrospective nature of the study, it was not possible to define the most acceptable dose of sunitinib; some patients received 50 mg daily for 4 weeks followed by a 2-week break, and others received 37.5 mg daily. The study concluded that sunitinib could be an effective treatment for MPPG. Nevertheless, these patients should have adequate blood pressure and pain control before and during treatment and supportive measures should be implemented to prevent and treat adverse effects such as mucositis, hand-and-foot syndrome, and fatigue. Two phase 2 clinical trials of sunitinib for patients with MPPG are currently active.

Two phase 2 studies attempted to assess pazopanib and axitinib as potential treatments for MPPG [10]. Recruitment was suboptimal, with 6 patients for pazopanib and 9 patients for axitinib. Some patients had tumor size reduction with treatment. However, several patients experienced gastrointestinal and serious cardiovascular adverse events. Cardiovascular adverse events occurred when doses were titrated up (trial design). The pazopanib trial was terminated and the axitinib trial is currently closed (www.ClinicalTrials.Gov). It is unclear whether data reported from these trials will add to the treatment options available to patients with MPPG.

Cabozantinib seems to be a more promising molecule. Patients with kidney cancer treated with cabozantinib exhibited better PFS and objective response rates than patients treated with sunitinib [52]; furthermore, in patients with bone metastases, cabozantinib is associated with palliation of pain, increased hemoglobin, and decreased bone turnover [53]. Inhibition of c-met may also delay the development of resistance to cabozantinib [54]. Preliminary results of a phase 2 study of cabozantinib in 11 patients with MPPG have shown that most patients had tumor size reduction and disease stabilization, and no serious adverse events have been reported to date [55•]. PFS was 11.2 months. The initial dose of cabozantinib is 60 mg daily and the dose is titrated down on the basis of tolerability.

Immunotherapy

MPPG use the hypoxia-pseudohypoxia to grow and survive. As observed in other cancers, this environment may prevent the immune system from recognizing the MPPG cells. Pembrolizumab, an antibody that blocks the program cell death protein (PD1), is under evaluation for the treatment of MPPG through a phase 2 clinical trial [10].

Treatment of Bone Metastasis: Focus on the Spine

Bone metastasis occurs in 70–80% of patients with MPPG irrespective of the primary tumor location and size, genetic background, and biochemical phenotype [25]. Bone metastasis represents one of the most overwhelming manifestations of MPPG, predisposing patients to skeletal-related events. Among patients with bone metastasis, 72% present with bone pain, pathologic fractures, and/or cord compression and frequently need radiation therapy and/or surgical intervention [25]. The risk of additional skeletal-related events is cumulative, and skeletal-related events often occur quickly (median time to recurrence is 4 months) [25]. Response to systemic

therapy (chemotherapy, MIBG, tyrosine kinase inhibitors) and treatment with antiresorptive therapies (zoledronic acid, denosumab) are associated with a reduced rate of skeletal-related events [25].

Surgical Treatment of Spine Metastasis

Conventional external beam radiation therapy (cEBRT) has been the most commonly prescribed treatment in patients with MPPG bone metastasis; however, the efficacy of this treatment is difficult to determine given the rarity of MPPG. Vogel et al. [56] reported that among 24 patients with MPPG treated with cERBT, more than 80% had symptomatic and imaging improvement.

Patients with epidural cord compression may benefit from receiving surgery as well as cERBT. A randomized controlled trial in patients with any cancer with spine metastasis [57•] showed that circumferential decompression and spine stabilization followed by cEBRT was superior to cEBRT alone. Patients who received both therapies exhibited a faster recovery of ambulation, better maintenance of sphincter continence, better pain control, and substantially improved performance status.

Recent advances in radiobiology and image guidance have led to the development of spinal stereotactic radiosurgery (SSRS), which allows the delivery of a single or hypofractionated high dose of radiation directly to the lesion, with the hallmark of a rapid decrease in toxic effects on adjacent tissue [58–60]. Nevertheless, in the setting of epidural disease resulting in spinal cord displacement, surgery is recommended as the first-line treatment for decompression and reconstitution of the cerebrospinal fluid column around the spinal cord. This allows adequate coverage of the gross target disease while minimizing the radiation delivered to the spinal cord [61, 62].

Instability of the Spine

A major advance in maintaining spinal stability in the setting of neoplastic disease has been the development of the Spine Instability Neoplastic Score [63] (Table 2). On the basis of the tumor location, pain characteristics, bone involvement, spinal alignment, degree of vertebral body collapse, and involvement of the posterior vertebral elements, patients are stratified into one of three main categories: stable, where no intervention is required; potentially unstable, where specialized surgical evaluation is recommended; or unstable, where surgical intervention is required. This tool has been evaluated prospectively and was found to be useful in guiding decision-making and referral for surgical evaluation to avoid catastrophic and painful neurologic outcomes [64, 65]. Spinal instability can be treated only with surgery. Compression fractures without disruption of the posterior vertebral body cortex can be safely treated with percutaneous cement injection, which is believed to restore the axial capacity of the failing anterior column [66]. Disruption of the dorsal wall of the vertebral body represents a relative contraindication to cement injection because this disruption can lead to risk of cement extravasation to the spinal canal. In such cases, pedicle screws can be inserted in the adjacent levels using a percutaneous technique that minimizes soft tissue disruption, resulting in a relatively rapid postoperative recovery [67]. Lastly, when severe kyphotic deformity and spinal cord compression are present, the best approach is open surgery for decompression and realignment of the spine

Table 2 Spinal Oncology Study Group Spine Instability Neoplastic Score (SINS) system [10]

SINS component	Score
Location	
Junctional (occiput–C2, C7–T2, T11–L1, L5–S1)	3
Mobile spine (C3–C6, L2–L4)	2
Semi-rigid (T3–T10)	1
Rigid (S2–S5)	0
Pain[a]	
Yes	3
Occasional pain but not mechanical	1
Pain-free lesion	0
Bone lesion	
Lytic 2	2
Mixed (lytic/blastic)	1
Blastic	0
Radiographic spinal alignment	
Subluxation/translation present	4
De novo deformity (kyphosis/scoliosis)	2
Normal alignment	0
Vertebral body collapse	
< 50% collapse	3
> 50% collapse	2
No collapse with 50% of body involved	1
None of the above	0
Posterolateral involvement of spinal elements[b]	
Bilateral	3
Unilateral	1
None of the above	0

Scores of 0 to 6 points are considered stable. Scores of 7 to 12 points are considered potentially unstable. Scores of 13 to 18 points are considered unstable. From Fisher CG, Schouten R, Versteeg AL, Boriani S, Varga PP, Rhines LD, Kawahara N, Fourney D, Weir L, Reynolds JJ, Sahgal A, Fehlings MG, Gokaslan ZL (2014) Reliability of the Spinal Instability Neoplastic Score (SINS) among radiation oncologists: an assessment of instability secondary to spinal metastases. Radiat Oncol 9:69. https://doi.org/10.1186/1748-717X-9-69

[a] Pain improvement with recumbency and/or pain with movement/loading of the spine

[b] Facet, pedicle, or costovertebral joint fracture or replacement with tumor

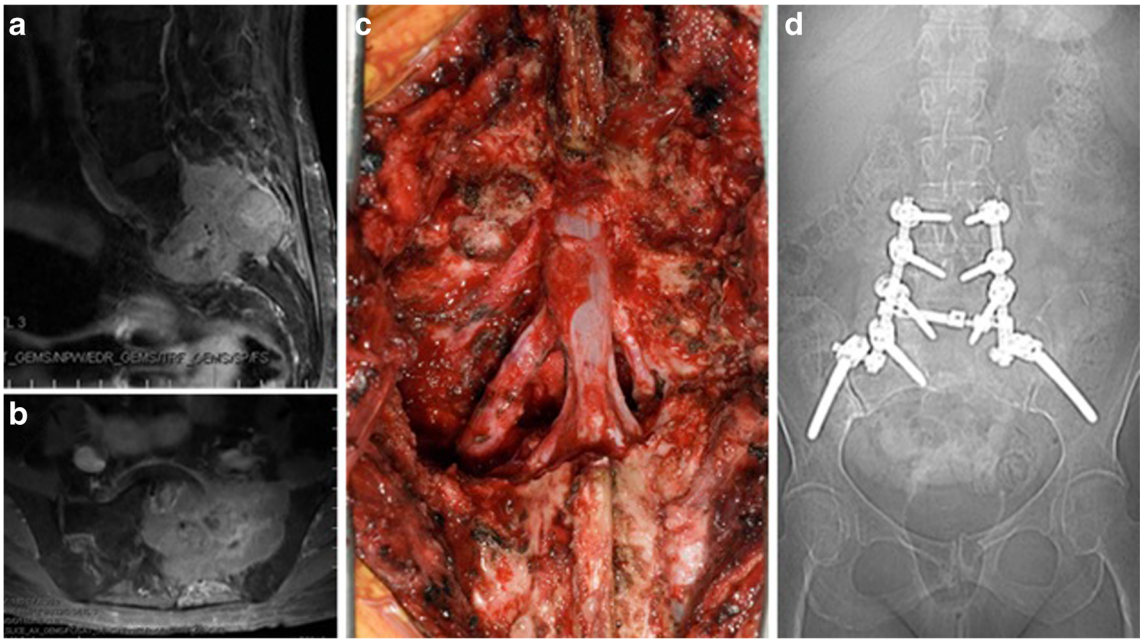

Fig. 1 Surgical treatment of metastatic pheochromocytoma to the spine. **a** Sagittal and **b** axial magnetic resonance images in a T1 sequence with contrast showing a large pheochromocytoma metastasis involving the L5 and S1 vertebral bodies, causing complete obliteration of the spinal canal and compression of the nerve roots. **c** Intraoperative picture demonstrating complete decompression of the thecal sac and lumbosacral nerve roots. **d** Anteroposterior x-ray showing the lumbopelvic fixation required to stabilize the spine after surgical resection of the tumor

with reconstruction of the anterior vertebral body and placement of dorsal instrumentation, generally two levels above and below the fracture (Fig. 1) [68–70].

Evaluation of Spinal Cord Compression

Bilsky et al. [71] proposed classifying the degree of spinal cord compression on the basis of axial magnetic resonance imaging in a T2 sequence (Fig. 2) when SSRS is considered. In this classification system, tumors in the vertebral bodies without epidural extension are grade 0, tumors with epidural extension without displacement of the dura are grade 1a, epidural tumors with mild displacement of the dura preserving the cerebrospinal fluid column anterior to the spinal cord are grade 1b, tumors with epidural extension displacing the dura and touching the spinal cord are grade 1c, tumors with

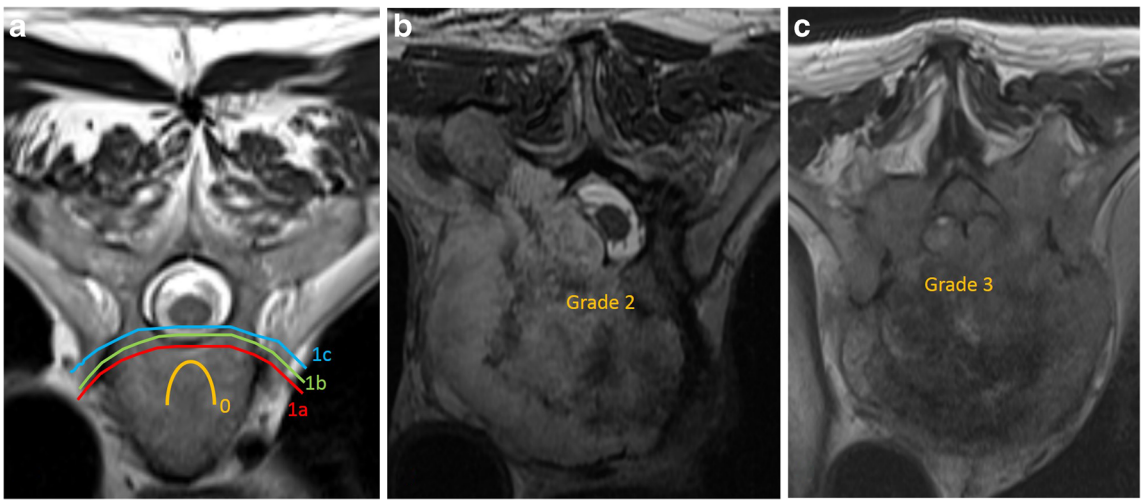

Fig. 2 Illustration of the ESCC grading scale. Grade 0: tumor in the vertebral bodies without epidural extension; grade 1a: initial epidural impingement, without deformation of the thecal sac; grade 1b: epidural tumor with mild displacement of the dura preserving the cerebrospinal fluid anterior to the spinal cord; grade 1c: tumors with epidural extension causing cord abutment without cord compression. Grade 2: tumor with epidural extension displacing the spinal cord but preserving some cerebrospinal fluid around the spinal cord. Grade 3: tumors associated with a complete absence of cerebrospinal fluid (myelographic blockage)

epidural extension displacing the spinal cord but preserving some cerebrospinal fluid around the spinal cord are grade 2, and tumors associated with a complete absence of cerebrospinal fluid (myelographic blockage) are grade 3. Grades 0–1b imply low-grade epidural compression, and these tumors can be treated with SSRS alone. Grades 1c–3 imply severe spinal cord compression, and these tumors require surgery to decompress the cord prior to SSRS.

Surgical Decompression of the Spinal Cord

Laufer et al. [72] proposed a very useful decision-making algorithm in which neurologic, oncologic, mechanical, and systemic factors are analyzed and the use of cEBRT, SSRS, and/or surgery is recommended on the basis of tumor sensitivity to radiation and the extent of epidural involvement. In this context, local control is achieved with radiation (cEBRT/SSRS) and surgery is used to remove the epidural tumor and stabilize the spine. The extent of surgical resection loses importance in terms of local control if tumoricidal doses of cEBRT or SSRS are delivered to the residual disease [61, 72]. Laufer et al. [73] also reported a 4.1% cumulative incidence rate of local progression with hypofractionated SSRS (24–30 Gy in three fractions) and a 9% cumulative incidence rate with SSRS delivered as a high single dose (24 Gy) after surgical decompression and stabilization. Our clinical experience suggests that a median interval of 2–3 weeks is required from the time of surgery to the start of radiation therapy. Systemic treatment is interrupted during this interval and resumed once radiation is completed.

Conclusion

Over the past 5 years, the progress on therapeutics for MPPG has been striking. Recent studies indicate that surgical resection of the primary tumor might decrease the risk of metastasis and improve OS despite advanced disease. Patients with bone metastasis may benefit from antiresorptive therapies, surgery, and SSRS. CVD chemotherapy may be indicated to treat patients with progressive disease, and patients who respond to CVD may benefit from a maintenance regimen with dacarbazine. Patients also now have other systemic therapeutic options to consider. Clinical trials are underway for radiopharmaceutical agents, tyrosine kinase inhibitors, and immunotherapies. Preliminary results of the phase 2 trial with Ultratrace iobenguane are impressive, and anti-angiogenic drugs may help treat MPPG. Our knowledge of genomics is increasing and novel options will continue to develop. A brighter future is ahead.

Compliance with Ethical Standards

Conflict of Interest Paola Jimenez, Claudio Tatsui, Aaron Jessop, Sonali Thosani, and Camilo Jimenez declare they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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