High incidence of morbidity following resection of metastatic pheochromocytoma in the spine

Report of 5 cases

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Pheochromocytomas of the spine are uncommon and require careful preoperative planning. The authors retrospectively reviewed the charts of 5 patients with metastatic spinal pheochromocytoma who had undergone surgical treatment over the past 10 years at their medical center. They reviewed patient age, history of pheochromocytoma resection, extent and location of metastases, history of alpha blockage, surgical level, surgical procedure, postoperative complications, tumor recurrence, and survival. Metastases involved the cervical (1 patient), thoracic (3 patients), and lumbar (2 patients) levels. Preoperative treatment included primary pheochromocytoma resection, chemotherapy, alpha blockade, embolization, and radiation. Three patients had tumor recurrence, and 2 underwent 2-stage reoperations for tumor extension. Hemodynamic complications were common: 2 patients developed pulseless electrical activity arrest within 4 months after surgery, 1 patient had profound postoperative tachycardia with fever and an elevated creatine kinase level, and 1 patient experienced transient postoperative hypotension and paraplegia. One patient died of complications related to disseminated cerebral and spinal disease.

With careful preoperative and surgical management, patients with symptomatic metastatic spinal pheochromocytoma can benefit from aggressive surgical treatment. Postoperative cardiovascular complications are common even months after surgery, and patients should be closely monitored long term.

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KEY WORDS • spinal pheochromocytoma • spinal tumor • en bloc • oncology

PHEOCHROMOCYTOMAS are rare, metabolically active tumors arising from the chromaffin cells of the adrenal medulla. In particular, they arise from chromaffin cells that secrete catecholamines into the systemic circulation. Exogenous norepinephrine and epinephrine from these tumors result in hemodynamic sequelae, such as palpitations, shortness of breath, hypotension, and tachycardia. Long-term endogenous overexposure to elevated serum catecholamines can lead to cardiac complications, such as worsening arrhythmias and cardiomyopathy. The majority of pheochromocytomas are benign or noninvasive and can be treated with surgical excision. Malignant forms account for 10%–20% of all cases and most commonly metastasize to the liver, lymph nodes, spleen, and lungs. Five-year survival rates range from 84% to 96% for benign pheochromocytoma, to less than 50% for malignant pheochromocytoma.

Although bony involvement and skeletal spread are well-described complications of malignant pheochromocytoma, the spine is a relatively uncommon site of metastasis. Clinical presentations can vary based on the primary source of the bone lytic lesions. Cases in the present report represent the largest series of spinal metastatic pheochromocytoma and feature outcomes, surgical approach, and postoperative management of alpha blockade. In a review of the literature, we discuss common preoperative considerations in patients with metastatic pheochromocytoma in the spine and how to manage postoperative hemodynamic complications. We previously reported a single case in the literature, and this patient is included in the present series.

Case Reports

Case 1

History and Examination. A 28-year-old healthy white man presented with abdominal and low-back pain. Imaging demonstrated an adrenal pheochromocytoma with additional lesions in L-3 and L-4. He underwent resection of the adrenal mass at the time of its initial diagnosis, but giv-
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en the absence of any neurological compromise, the metastatic lesions were not resected. The patient then received chemotherapy with cisplatin and zoledronic acid, which was ultimately ineffective in controlling his metastatic disease. A vertebroplasty was subsequently performed to prevent vertebral body collapse. He remained symptom free until 4 years following his initial diagnosis, at which time surveillance CT of the lumbar spine demonstrated significant progression of the spinal disease (Fig. 1A).

Treatment. The patient began alpha blockade with phenoxybenzamine and metyrosine as well as blood pressure control with atenolol 1 month prior to surgery and underwent preoperative embolization of the vascular supply to the L-3 and L-4 vertebral bodies (Fig. 1B). He subsequently underwent a 2-stage procedure, requiring 6 units of transfused blood throughout both stages, with an estimated blood loss of 4100 ml despite preoperative embolization.

Posttreatment Course. He remained neurologically intact throughout his postoperative course; however, after the second stage of the procedure, he developed tachycardia in the 160s (bpm), fever of 39.8°C, and elevated creatine kinase (CK; 11,704 U/L, reference range 24–195 U/L). An endocrine consult was sought to rule out pheochromocytoma multisystem crisis. The patient is 21 months out from surgery and remains neurologically intact without further recurrence or additional metastatic disease. He is 4 years out from the diagnosis of spinal metastatic disease.

Case 2

History and Examination. A 41-year-old white man with a history of atrial fibrillation and deep venous thrombosis treated with anticoagulation presented with upper-back pain. On CT and MRI studies, he had evidence of multiple lesions in his T5–7 vertebrae, a paraspinal lesion at T-4, multiple hemangiomas in the lumbar spine, and a mass in his sacroiliac joint (Fig. 2A). Biopsy of the spinal lesion was consistent with a pheochromocytoma, and he was started on phenoxybenzamine and metyrosine for alpha blockade.

He underwent radiation followed by a T5–7 decompression, costotransversectomy with intrallesional vertebrectomy from T-5 to T-7, and posterior instrumentation from T-3 to T-10 (Fig. 2B). Postoperatively, he remained on alpha blockade pending adrenalectomy. Three years after his initial spine surgery, he underwent resection of the primary pheochromocytoma. He received further chemotherapy with Cytoxan, vincristine, and dacarbazine without evidence of further disease progression. Four years after his first spine surgery, imaging revealed metastatic disease at the T-1 vertebral body with epidural extension.

Treatment. One week prior to surgery the patient was started on phenoxybenzamine and metyrosine for preoperative alpha blockade. Preoperative embolization was performed and followed by a 2-stage procedure: a posterior C4–T10 instrumentation and an anterior sternotomy for vertebral body resection at T-1 with cage placement. Intraoperatively, the patient experienced no hemodynamic complications.

Posttreatment Course. On the evening following the second surgical procedure, the patient experienced an episode of atrial fibrillation with rapid ventricular response, hypotension, and tachycardia in the 160s. His phenoxybenzamine and metyrosine were discontinued, and blood pressure control was attained with diltiazem. Ultrasound demonstrated a nonocclusive clot in the jugular vein. He was discharged to rehabilitation on anticoagulation. On postoperative Day 11, he presented to the emergency room with shortness of breath and pulseless electrical activity (PEA) arrest due to cardiac tamponade. The patient was urgently intubated and underwent pericardial drainage that yielded 1300 ml of bloody fluid. He remained stably tachycardic in the 110s throughout his admission.

Eighteen months after his surgery at T-1, an epidural

![Fig. 1. A: Preoperative sagittal CT scan revealing previous 2-level vertebroplasty at L-3 and L-4. There is a significant loss of height of the L-4 vertebral body. B: Coronal angiogram demonstrating bilateral coils following preoperative embolization. C: Postoperative CT scan showing a ventral cage construct replacing the L3–4 vertebral bodies with posterior hardware from L-1 to the pelvis.](image-url)
metastasis extending from C-2 to C-7 with spinal cord compression had developed (Fig. 2C). The patient was started on metyrosine and phenoxybenzamine 2 weeks prior to surgery and underwent a C2–6 laminectomy along with resection of the epidural tumor at C3–7. He had no intra- or postoperative complications but returned to the emergency room with an upper extremity deep venous thrombosis and a small pulmonary embolus. He was discharged to home on anticoagulation. Three months later, 6 years after his initial spine surgery, he died from complications of systemic disease.

Case 3

History and Examination. A 21-year-old previously healthy African American woman was diagnosed with widely metastatic pheochromocytoma after having severe hypertension at the end of her pregnancy, which was originally diagnosed as preeclampsia. On imaging she was found to have a 16-cm mass in the right adrenal gland and metaiodobenzylguanidine (MIBG)-positive lesions in the spine, sacrum, and femur. She was started on phenoxybenzamine and metoprolol for pretreatment alpha blockade in preparation for resection of the primary adrenal lesion; however, the lesion was only partially surgically debulked given its adherence to the vena cava and invasion of the liver. Three months following this initial diagnosis, the patient was noted to have epidural metastatic disease from C-7 to T-2 (Fig. 3A and B).

Treatment. She was taken to the operating room for an emergent posterior decompression and fusion from C-3 to T-7 with intralesional resection of the epidural tumor (Fig. 3C).

Posttreatment Course. She continued treatment with MIBG and zoledronic acid infusion. She remained tachycardic in the 110s at the clinical follow-up 1 month after surgery.

She received chemotherapy with vincristine, dacarbazine, and cyclophosphamide. Two and a half years after surgery for the spinal metastasis, she was found to have dura-based brain metastases causing midline shift and thrombi in the posterior sagittal and straight sinus (Fig. 3D). She received whole-brain radiation and external beam radiation to her neck, lumbar spine, and pelvis for palliative treatment of her metastatic lesions. Three years after the original diagnosis of pheochromocytoma, she underwent T4–7 laminectomy without extension of her instrumentation. Four months after her second spine surgery, she presented to the emergency room in PEA arrest attributed to profound anemia with a hemoglobin level of 3.9. She was resuscitated without neurological recovery, and care was withdrawn.

Case 4

History and Examination. A 62-year-old healthy white woman experienced palpitations, shortness of breath, and hypertension and was diagnosed with adrenal pheochromocytoma. Four and a half years after surgery for the primary pheochromocytoma, she developed recurrent symptoms, and imaging demonstrated widely metastatic disease in the cervical spine, liver, rib cage, lung, and L-1 vertebral body with epidural extension. She was maintained on phenoxybenzamine and zoledronic acid to manage her symptoms.

Treatment. Approximately 6 years after the initial diagnosis of pheochromocytoma, she had preoperative embolization (Fig. 4A) of the spinal tumor with subsequent hemorrhage around the embolization site. She then underwent a left lateral retroperitoneal L-1 corpectomy with resection of the epidural component and fusion from T-12 to L-2 (Fig. 4B and C). This was a single-stage procedure. No intraoperative hemodynamic complications were noted. She remained neurologically intact.

Posttreatment Course. She has continued on chemo-
therapy and radiation therapy for her metastatic disease in the cervical and thoracic spine. She is 1 year out from the spine surgery and 5.5 years out from the diagnosis of pheochromocytoma.

Case 5

History and Examination. A 23-year-old hypertensive white man had a history of malignant adrenal pheochromocytoma originally diagnosed and resected when he was 11 years old. He presented with bloody stool and back pain, and subsequent imaging demonstrated metastatic disease in the pelvis, lung, and neck. In addition, there was a focus of disease within the T-10 vertebral body (Fig. 5A and B). He had received 2 cycles of chemotherapy and radiation to the T-10 lesion but had progressive pain in the thoracic spine and an increasing need for antihypertensive medication. Surgery was offered for this lesion in the setting of a stable metastatic burden for symptom relief.

Treatment. He received preoperative alpha blockade with phenoxybenzamine and underwent embolization of the right-sided T-9 and T-10 intersegmental arteries. He then underwent a posterior T7–11 fusion with T-10 en bloc vertebrectomy and cage placement (Fig. 5C). No intraoperative hemodynamic changes were noted.

Posttreatment Course. In the immediate postoperative period, he experienced significant hypotension (70 mm Hg systolic) and rapidly progressive lower limb weakness. He was treated with a dopamine drip to increase his mean arterial pressure to 85 mm Hg, and his impending paraplegia resolved. Postoperative MRI showed no evidence of hematoma or hardware failure as the cause of his transient weakness. The surgeon posited that resection of the sympathetic chain ganglia during en bloc resection may have contributed to the postoperative hypotension. The patient’s severe preoperative hypertension resolved completely following tumor resection, and his condition remains controlled off all medication 1 year out from spinal surgery. He is 13 years out from the original diagnosis of pheochromocytoma and remains neurologically intact.

Summary of Cases

Patient demographic and outcome data are presented in Table 1. The average age was relatively young at 36 years (range 21–68 years). All patients presented with pain, and one presented with preoperative weakness due to epidural spinal compression. The location of the pheochromocytoma metastases varied, ranging from the lower cervical spine to the lower lumbar spine. Two patients presented with epidural extension, with one having associated paraparesis. All but one of the patients had received treatment with chemotherapy or undergone adrenal tumor resection and/or radiation before undergoing surgery for the metastasis. Embolization was performed preoperatively in 3 patients. En bloc resection was performed in 2 cases (1 and 5), while intralesional resection was involved in the remaining cases.

No intraoperative hemodynamic changes occurred in any case; however, postoperative hemodynamic complications were common (Table 1). The patient in Case 1 experienced postoperative tachycardia, fever, and elevated CK level suggestive of a systemic crisis. In their postoperative courses, the patients in Cases 2 and 3 developed PEA arrest related to cardiac tamponade and profound anemia, respectively. The patient in Case 5 was notable for immediate postoperative hypotension responsive to fluids and pressors. Three of the 5 patients demonstrated recurrent...
disease after resection that was not affected by either en bloc or intralesional resection. Patients in Cases 2 and 3 died during the follow-up period, and the patient in Case 1 required reoperation for tumor extension. Three of the 5 patients remained alive when this paper was written.

**Discussion**

Pheochromocytomas are among the most serious neuroendocrine disorders because of the risk of systemic complications secondary to active catecholamine secretion. Cardiovascular sequelae have been well documented in the literature and include cardiac hypertrophy, dilated cardiomyopathy, ischemic heart disease, myocardial infarction, cardiac arrhythmias, and cardiogenic shock. Persistent hemodynamic instability in the absence of catecholamine crises has been attributed to long-lasting vascular changes. Remodeling of the blood vessels has been shown to occur with prolonged sympathetic stimulation, thereby placing the patient at greater risk for a cardiovascular event. Sustained elevated levels of circulating catecholamines contribute to vascular damage with subsequent remodeling and arteriosclerosis.

The current literature indicates that the risk of severe hemodynamic instability is most prominent during resection of an active lesion, as significant fluctuations in blood pressure or the heart rate can occur during anesthesia induction or tumor manipulation. A large tumor size, high systolic pressures, and high preoperative urine metanephrine concentrations have been associated with increased and prolonged incidences of intraoperative hypertension. However, intraoperative hemodynamic
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TABLE 1: Summary of preoperative exposure and postoperative complications for all patients*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Embolization</th>
<th>Resection of Primary Lesion†</th>
<th>Postop Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33, M</td>
<td>yes</td>
<td>yes</td>
<td>tachycardia (160s), fever (39.8°C), elevated CK level</td>
</tr>
<tr>
<td>2</td>
<td>45, M</td>
<td>yes</td>
<td>yes</td>
<td>pulmonary emboli, cardiac tamponade, PEA arrest, 3 separate spine lesions (T-5, T-1, epidural cervical spine), death</td>
</tr>
<tr>
<td>3</td>
<td>23, F</td>
<td>no</td>
<td>no</td>
<td>brain metastases, recurrence at caudal aspect of previous surgery, PEA arrest, death</td>
</tr>
<tr>
<td>4</td>
<td>68, F</td>
<td>yes</td>
<td>yes</td>
<td>none reported</td>
</tr>
<tr>
<td>5</td>
<td>23, M</td>
<td>yes</td>
<td>yes</td>
<td>transient hypotension &amp; paraplegia; resolved w/ dopamine</td>
</tr>
</tbody>
</table>

* All patients received alpha blockade, which included treatment with phenoxybenzamine with or without metyrosine for 2 weeks or more before spine surgery.
† Resection of primary lesion indicates surgical excision of the primary adrenal pheochromocytoma before the spinal surgery.

For Case 3, a primary resection attempt was made; however, the tumor had infiltrated the liver and inferior vena cava and was determined to be unresectable.

Complications resulting from the resection of metastatic spinal lesions are rare. This could be attributed to the routine use of preoperative alpha blockade and embolization, which has been associated with decreased surgical morbidity, reduced blood loss and transfusions, and shorter hospital stays.1,3,26,31

All 5 patients in our cohort received alpha blockade with phenoxybenzamine with or without metyrosine for at least 2 weeks prior to surgery, and 3 underwent preoperative embolization. None of the patients experienced intraoperative hemodynamic instability.

However, postoperative hemodynamic complications occurred in 4 of the 5 patients: tachycardia (Case 1); pulmonary emboli, hemopericardium, and cardiac tamponade (Case 2); PEA attributed to profound anemia (Case 3); and transient hypotension resulting in temporary paraparesis (Case 5). Note that the patients in Cases 2 and 3 experienced PEA after discharge from the hospital, a complication that has rarely been described in the context of pheochromocytoma. No reports of postoperative PEA arrest after resection of spinal metastases of pheochromocytoma are available in the MEDLINE index, and it is unclear what role the metastatic pheochromocytoma played in the pathogenesis of the PEA arrests.

Further, the patient in Case 2 most likely developed hemopericardium and subsequent tamponade because of a complex surgical approach, whereas the PEA arrest in the patient in Case 3 was attributed to profound anemia and perhaps narrow invasion of the metastatic process. Note that abnormal coagulation has been reported as a complication of endocrine disregulation,29 and it is possible that chronic exposure to elevated catecholamines altered the patient’s baseline substrate. Future studies and larger patient cohorts are needed to make definitive conclusions.

It is unclear if abnormal coagulation or underlying cardiovascular remodeling is the only cause of the observed postoperative complications; however, evidence from this cohort strongly suggests that long-term exposure to elevated catecholamines in cases of metastatic pheochromocytoma is associated with abnormal coagulation, bleeding, cardiovascular compromise, and blood pressure fluctuations.

Though resection is the most effective treatment for pheochromocytoma, our data suggest that careful, long-term postoperative monitoring is required for this patient population. Even after hormone levels have normalized and symptoms are reduced, the patient’s ability to cope with systemic challenge will probably be compromised. In a long-term follow-up study of 95 patients with adrenal or extraadrenal disease, Noshiro et al. described 3 patients who demonstrated normal plasma catecholamine levels postoperatively but died of stroke, myocardial infarction, or dissecting aneurysms.21 Thus, long-term surveillance is warranted to identify signs of cardiac instability or hemodynamic arrest, as well as to screen for tumor recurrence.

Though a survival benefit from the resection of malignant pheochromocytomas is still unproven, reducing the tumor burden can alleviate symptoms, as well as facilitate subsequent chemo- or radiation therapy.1,22 Most studies of spinal metastases have shown a postoperative improvement in blood pressure, headaches, palpitations, and anxiety; delayed complications have usually been associated with tumor recurrence or distant metastasis.31,13,15,33 We demonstrated that en bloc resection in one of our patients (Case 5) was associated with postoperative hypertensive crisis.12 The reasons for this are unknown but may be related to a reduction in the tumor burden and subsequent decrement in catecholamine secretion. Additionally, it may be related to the required cutting of bilateral sympathetic ganglia in the thoracic spine, inhibiting vasoconstriction. From this case, we also note that the risk of hypotensive crisis following complete tumor removal in the setting of ongoing adrenergic blockade can be severe enough to cause transient neurological deficits. Moreover, the role of en bloc vertebrectomy for metastatic lesions of the spine can be expanded for metastatic pheochromocytomas, as patients may show durable tumor and metabolic control of their disease. With appropriate and timely medical and surgical therapy, along with appropriate preoperative treatment strategies, patients with metastatic spinal pheochromocytomas can have long life expectancies. In Table 2, we review the steps for pre-, intra-, and postoperative management of metastatic pheochromocytoma.
**TABLE 2: Management of metastatic spinal pheochromocytoma**

<table>
<thead>
<tr>
<th>Preoperatively</th>
<th>Intraoperatively</th>
<th>Postoperatively</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preop embolization can reduce intrapatient blood loss</td>
<td>en bloc resection</td>
<td>Monitor for postop hypotension, which may present as worsening neurological deficit; inform ICU staff of possible risk</td>
</tr>
<tr>
<td>Alpha blockade w/ phenytoin &amp; metyrosine if disease metabolically active</td>
<td>Carefully monitor hemodynamic parameters &amp; notify anesthesiologist if tumor capsule violated</td>
<td>Discontinue preop alpha blockade if en bloc resection achieved</td>
</tr>
</tbody>
</table>

* ICU = intensive care unit.

**Conclusions**

No standard paradigm exists for the surgical management of symptomatic spinal pheochromocytomas. In addition to a full analysis of the extent of metastasis and life expectancy, careful preoperative workup in coordination with endocrine services must be done. Management should include preoperative embolization of the vascular supply to these tumors if it can be safely achieved, chemotherapy and/or radiation therapy in consultation with radiation oncology services, and/or resection of the primary adrenal tumor. Neurosurgical management depends on patient presentation and location of the metastasis with associated deformity and/or neural compromise. Preoperative alpha blockade is recommended, and surgery can include en bloc vertebrectomy, vertebroplasty, anterior or posterior decompression and fusion, and tumor resection. With appropriate treatment, long-term survival with neurological improvement for compressive metastatic disease is possible. Postoperative management must take into consideration any predisposing factors for hemodynamic complications, and long-term surveillance is warranted to screen for cardiovascular abnormalities and tumor recurrence.

**Disclosure**

Dr. Gokaslan has direct stock ownership in Spinal Kinetics and US Spine; has received clinical or research support from AO North America, NREF, and DePuy for the study described; and has received support from AO Spine, NREF, and AO Foundation for non-study-related clinical or research effort. Dr. Scibba is a consultant for Medtronic, DePuy-Synthes, Globus, and NuVasive. Dr. Witham has received support from Eli Lilly and Co. for non-study-related clinical or research effort.

Author contributions to the study and manuscript preparation include the following. Conception and design: Kim, Wolinsky, Scibba. Acquisition of data: Kalooostian, Zadnik, Kim, Groves, Wolinsky, Scibba. Analysis and interpretation of data: Kalooostian, Zadnik, Kim, Groves, Wolinsky, Scibba. Drafting the article: Kalooostian, Zadnik, Groves, Gokaslan, Bydon, Scibba. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Scibba.

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