

# En Bloc Resection of Solitary Functional Secreting Spinal Metastasis

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## Abstract

### Keywords

- ▶ functional secretory tumor
- ▶ spine
- ▶ metastasis
- ▶ en bloc
- ▶ surgery
- ▶ choriocarcinoma
- ▶ pheochromocytoma
- ▶ carcinoid

**Study Design** Literature review.

**Objective** Functional secretory tumors metastatic to the spine can secrete hormones, growth factors, peptides, and/or molecules into the systemic circulation that cause distinct syndromes, clinically symptomatic effects, and/or additional morbidity and mortality. En bloc resection has a limited role in metastatic spine disease due to the current paradigm that systemic burden usually determines morbidity and mortality. Our objective is to review the literature for studies focused on en bloc resection of functionally active spinal metastasis as the primary indication.

**Methods** A review of the PubMed literature was performed to identify studies focused on functional secreting metastatic tumors to the spinal column. We identified five cases of patients undergoing en bloc resection of spinal metastases from functional secreting tumors.

**Results** The primary histologies of these spinal metastases were pheochromocytoma, carcinoid tumor, choriocarcinoma, and a fibroblast growth factor 23–secreting phosphaturic mesenchymal tumor. Although studies of en bloc resection for these rare tumor subtypes are confined to case reports, this surgical treatment option resulted in metabolic cures and decreased clinical symptoms postoperatively for patients diagnosed with solitary functional secretory spinal metastasis.

**Conclusion** Although the ability to formulate comprehensive conclusions is limited, case reports demonstrate that en bloc resection may be considered as a potential surgical option for the treatment of patients diagnosed with solitary functional secretory spinal metastatic tumors. Future prospective investigations into clinical outcomes should be conducted comparing intralesional resection and en bloc resection for patients diagnosed with solitary functional secretory spinal metastasis.

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## Introduction

Metastatic tumors to the spine comprise a significant health burden to patients with cancer worldwide, with ~10 to 30% of patients developing symptomatic metastases over their lifetime and up to 90% of patients with terminal disease demonstrating evidence of metastatic disease on postmortem examination.<sup>1-3</sup> The most common tumor types that metastasize to the spine are breast, lung, and prostate; however, rarer tumor subtypes have been shown to metastasize to the vertebral column. The most common indications for which patients undergo palliative surgical resection are intractable pain, instability or impending instability, local tumor control, and/or neurologic deficit. With the rarer tumor subtypes, the indication for surgical resection may be based on intrinsic tumor properties that have the potential to result in increased morbidity and mortality for patients.

Functional secretory tumors can produce hormones, growth factors, peptides, and/or molecules into the systemic circulation, contributing a distinct additional set of associated morbidities and potentially increased mortality. For instance, pheochromocytomas produce excess epinephrine, norepinephrine, and dopamine resulting in symptoms ranging from anxiety, chest and abdominal pain, weight loss, orthostatic hypotension, hyperglycemia, and transitory electrocardiographic changes.<sup>4</sup> Phosphaturic mesenchymal tumor mixed connective tissue variant can cause tumor-induced osteomalacia, which is a rare paraneoplastic syndrome caused by renal phosphate wasting resulting in a defect in vitamin D metabolism, phosphaturia, and osteomalacia.<sup>5-7</sup> Adrenocorticotropic hormone and/or corticotropin-releasing hormone syndromes can lead to Cushing syndrome and are shown to be associated with carcinoid tumors, small cell lung carcinomas, pheochromocytomas, and more rarely medullary thyroid carcinomas, nephroblastomas, pancreatic carcinomas, gastrointestinal adenocarcinomas, and even prostate cancer metastases.<sup>8</sup> Similarly, although growth hormone-secreting pituitary adenomas are generally benign, distant metastases are shown to occur, although rarely.<sup>4,9</sup> Each of these tumor subtypes can have a wide range of effects systemically and additionally are associated with increased morbidity and poor quality of life.

The secretory nature of functional tumors can result in serious and sometimes deadly adverse events, prior to any intervention and especially during surgical manipulation of the tumor.<sup>4</sup> For instance, during intraserial resection of a pheochromocytoma, massive catecholamine release (>1,000 times the normal plasma concentration) can occur resulting in hypertensive crisis, arrhythmias, stroke, myocardial infarction, or multiorgan failure.<sup>4,10</sup> Although surgical resection may appear to be complete, functional tumors may continue to secrete clinically relevant quantities of secretory molecules in the presence of microscopic residual disease. To provide long-term control and a possible cure, surgical strategies that eliminate the secretory molecule while preventing the potential for microscopic residual disease to persist should be employed.

En bloc resection with a wide margin, or the surgical removal of a tumor encased by a continuous outer margin

of healthy tissue in one intact specimen without breaching the tumor capsule, is considered the preferred treatment option for aggressive primary tumors.<sup>11</sup> En bloc resection has a limited role in the treatment of metastatic spine disease due to fact that systemic burden usually determines morbidity and mortality. However, for secretory tumors, en bloc resection may be the ideal treatment to obtain a metabolic cure in patients diagnosed with solitary functional secreting spinal metastasis because the tumor can be resected without spilling tumor cells and/or the secretory agent into the resection cavity. Thus, en bloc resection has the potential to reduce local recurrence and eliminate the systemic effects and/or symptomatology associated with the involved secretory factor. In this article, we review the literature on en bloc resection of functionally active spinal metastases and demonstrate that en bloc resection may be considered as a potential surgical option for the treatment of patients diagnosed with secretory hypermetabolic tumors. The purpose of this study was to evaluate the role of en bloc resection of functionally active spinal metastases in decreasing local recurrence rates and improving progression-free survival when compared with the traditional surgical methods.

## Methods

### Literature Search

A review of the literature was performed utilizing PubMed and a review of the bibliographies from the reviewed articles. The search query was broad and formulated to combine several subheadings and keywords that included the therapies and pathologies of interest. The search string employed was the following: (“en bloc resection”) AND (“Neoplasm Metastasis”[Mesh] OR Metasta\*) AND (“Spine”[Mesh] OR “Spinal Cord Neoplasms”[Mesh] OR “Vertebral Column” OR “Vertebral Columns” OR “Spinal Column” OR “Spinal Columns” OR “Vertebra” OR “Vertebrae” OR “Vertebral” OR “Intervertebral” OR “Spine” OR “Spinal” OR “Epidural” OR “Sacrum” OR “Sacrum” OR “Coccyx” OR “Cervical” OR “Epistropheus” OR “Odontoid Process” OR “Odontoid Processes” OR “annulus fibrosus” OR “nucleus pulposus” OR “Choriocarcinoma” OR “pheochromocytoma” OR “human chorionic gonadotrophin ” OR “growth factor” OR “carcinoid” OR “Adrenocorticotropic ” OR “growth hormone” OR “growth factor” OR “osteomalacia” OR “parathyroid hormone”).

### Eligibility Criteria

The criteria for potential inclusion in this review were: (1) articles published between 1980 and 2011, (2) all articles in English or with an English translation, (3) adult subjects (18 years and older), (4) articles describing the use of en bloc resection in the treatment of metastatic disease, (5) functional or secretory tumors, (6) spine metastasis, (7) fully published peer-reviewed studies including case reports randomized controlled trials, nonrandomized trials, cohort studies, case control studies, case series, and prospective and retrospective studies. We excluded articles describing (1) intradural spine tumors, (2) leptomeningeal disease following surgical resection, and (3) pediatric subjects, and (4)

articles with no extractable data specific to metastatic spine disease were also excluded.

The abstracts were screened by two independent reviewers using the inclusion and exclusion criteria described. Reviewer disagreements were resolved by a third reviewer. Full-text versions of acceptable articles were gathered and subjected to more-detailed screening for inclusion. After finalizing a collection of eligible studies, the studies were analyzed in detail, and the data pertaining to the research questions was extracted and tabulated by one reviewer. The second reviewer checked the extracted information.

### Data Extraction

We collected demographic and preoperative data from each of the eligible studies, including age, gender, primary tumor histology, secreted factor, location and number of levels involved, preoperative symptoms, and preadjuvant therapies. With respect to the operative approach and postoperative outcomes, we also collected information on the surgical approach, vertebral levels resected, presence or absence of an expandable cage, levels of fusion, change in neurologic function, time to recurrence, and overall survival.

## Results

### Intralesional Resection of Metastatic Functional Spine Tumors

Several case reports of spinal metastasis causing tumor-induced osteomalacia undergoing some form of surgical intervention have been reported to date.<sup>7,12-15</sup> The metastatic lesions were found throughout the vertebral column and had diagnoses of phosphaturic mesenchymal tumor mixed connective tissue variant, neuroendocrine tumor, osteosarcoma, osteoblastoma, and plasmacytoma. Boriani and Campanacci reported a case of osteoblastoma associated with osteomalacia in 1978.<sup>12</sup> Stone et al described a neuroendocrine tumor in the thoracic spine of a 33-year-old woman,<sup>16</sup> and Terek and Nielsen described an osteosarcoma in the sacrum causing osteomalacia, which was treated with neoadjuvant chemotherapy and intralesional excision, with no evidence of recurrence 11 months after surgery.<sup>14</sup> Chua et al demonstrated a case of solitary plasmacytoma in the T3 vertebral body causing tumor-induced osteomalacia. The lesion was surgically resected; however, the patient required several further surgeries for bone grafting secondary to instability and had local recurrence of the lesion 15 years after initial resection.<sup>13</sup> Gandhi et al reported the case of a 66-year-old woman with tumor-induced osteomalacia caused by fibroblast growth factor 23-secreting mesenchymal tumor who underwent an anterior L4 total spondylectomy with normalization of her serum phosphorous levels at 6-month follow-up.<sup>7</sup>

In terms of other functional secretory tumors treated via surgical resection, Dayan et al described a complete biochemical and radiologic cure of treatment-resistant acromegaly following resection of a somatotroph-producing pituitary carcinoma that was metastatic to the cervical spine.<sup>17</sup> Sciubba et al reported a 68-year-old woman with a solitary metastasis

of Hürthle cell carcinoma to the T1 vertebral body causing severe kyphotic deformity, myelopathy, pain, and an elevated thyroglobulin level.<sup>18</sup> She was treated with intralesional surgical resection and instrumented fusion. Unfortunately, many of these studies do not report the time to recurrences or overall survival.

In terms of pheochromocytoma, one case series and several case reports described the clinical course of patients who had intralesional resection. Kaloostian et al described three patients in their case series who underwent intralesional resection.<sup>19</sup> A 41-year-old man with multiple lesions in the T5–T7 vertebrae underwent radiation followed by a T5–T7 decompression, with intralesional vertebrectomy. Postoperatively, he received chemotherapy, and 4 years after his initial spinal surgery, he presented with metastatic disease at T1. He underwent preoperative embolization followed by a two-staged posterior C4–T10 fusion and T1 vertebral body resection with cage placement. After his second surgery (postoperative day 11), he presented in pulseless electrical activity arrest secondary to cardiac tamponade and died 3 months later from complications of systemic disease. They also described a 21-year-old woman diagnosed with metastatic disease during pregnancy who underwent C3–T7 posterior decompression and fusion, followed by chemotherapy. She underwent a second spinal surgery with a T4–T7 decompression for metastatic progression, but 4 months later she died after presenting in pulseless electrical activity arrest from profound anemia. In their last case, Kaloostian et al described a 62-year-old woman who underwent a retroperitoneal L1 corpectomy with T12–L2 fusion followed by radiation and chemotherapy for widely metastatic disease; the patient was still alive at 1-year follow-up.<sup>19</sup> Kasliwal et al described a patient who required two surgical debulking procedures of a recurrent thoracic pheochromocytoma over a 6-year period, with eventual death 6 months after the last resection.<sup>20</sup> Scalfani et al reported excision of the extradural component of a thoracic metastatic pheochromocytoma in a patient with disseminated disease who died 26 months after surgery.<sup>21</sup>

### En Bloc Resections for Functional Spine Mets

The utility of en bloc resections in the treatment of functionally active secretory tumors has been demonstrated in several case reports that have described various tumor subtypes and clinical syndromes. Kaloostian et al reported the first case of en bloc excision of a T10 vertebral body pheochromocytoma in a 23-year-old man.<sup>22</sup> The patient underwent angiographic embolization followed by a single-stage posterior en bloc vertebrectomy with placement of a cage, posterior instrumentation, and fusion. The patient had a temporary hypotension-associated neurologic decline that resolved completely after correction of the hypotension postoperatively. One year after surgery, the patient had no evidence of spinal tumor recurrence. Although this case demonstrates the role of en bloc spondylectomy in the treatment of patients with actively secreting tumors, the authors also concluded that en bloc resection may help prevent the complications of intraoperative hypertensive crisis commonly associated with pheochromocytoma and potentially alleviate the future need

for adrenergic medication.<sup>22</sup> Kaloostian et al also reported a 28-year-old man with abdominal and low back pain who presented with pheochromocytoma metastatic to the L3 and L4 vertebral bodies. He underwent an en bloc resection and fusion and had one episode of presumed pheochromocytoma multisystem crisis postoperatively; however, he remained neurologically intact with no further symptoms and no evidence of recurrent disease 21 months after surgery (► **Table 1**).<sup>19</sup>

Other case reports have described surgical treatment via an en bloc approach with elimination of the functional secretory tumor as the primary indication. These reports utilized the serum levels of the associated secretory molecule to determine recurrence after resection. Naito et al highlighted a 38-year-old woman who presented with abnormal uterine bleeding and high serum levels of human chorionic gonadotrophin and was found to have an L2 choriocarcinoma metastasis.<sup>23</sup> They performed an en bloc spondylectomy after a poor response to chemotherapy with methotrexate. Following the en bloc resection, the serum level of human chorionic gonadotrophin increased, and she developed local recurrence at the L2 vertebra as well as epidural extension. This patient had excessive intraoperative bleeding during the first stage of the operation and underwent embolization prior to the second stage (an anterior procedure). The tumor recurred 2 months after surgery and the patient eventually died secondary to metastatic tumor progression 3 months after surgery. Narayanan report the case of a 50-year-old woman who presented with a 4-month history of numbness and mild left hand weakness. The patient underwent a C7–T1 en bloc resection of a carcinoid tumor and had no evidence of recurrence at 6 years' follow-up.<sup>24</sup> En bloc spondylectomy was performed on a 56-year-old woman with tumor-induced osteomalacia secondary to a fibroblast growth factor 23-secreting phosphaturic mesenchymal tumor in the T8 vertebral body. The en bloc resection successfully treated this metabolically active tumor and resolved her tumor-induced osteomalacia, with fibroblast growth factor 23 levels returning to normal 14 months after surgery (► **Table 1**).<sup>15</sup>

## Discussion

Medical management is often first-line therapy for patients diagnosed with metabolically active functional secretory tumors. For certain tumor subtypes, control of the secretory molecule and/or the tumor-induced symptoms are the priorities in patient management. In cases of disseminated disease and/or failure of medical management, other treatment options are considered to control symptoms and/or control the disease burden to improve quality and potentially quantity of life. For functional tumor metastases to the spine, surgical intervention can be pursued in the appropriate situations where resection can control tumor-induced symptoms, stabilize the vertebral column, and/or offer a potential cure. Functional tumors exert their effects via the secretion of hormones and/or factors into the systemic circulation, causing hemodynamic instability, metabolic derangements, aberrant growth, and/or subjective symptoms that decrease the

overall quality of life of patients diagnosed with these malignancies. Patients diagnosed with functional tumor spinal metastases are often treated with medical management and/or adjuvant therapies.<sup>4,25</sup> In the appropriate situations, surgical intervention can be considered as the most definitive method for alleviating a patient's symptoms through effective removal of the offending lesion. Several case reports have demonstrated that intralesional surgical resection for functional tumor spinal metastasis has some benefit; however, the prognosis often remains dismal.<sup>20,21</sup>

En bloc resection may be advantageous in the resection of solitary functional secretory metastases. En bloc resection aims to surgically remove a tumor in one piece without violating the tumor capsule. In cases of primary malignant tumors, en bloc excision is frequently attempted with a wide margin excision, which describes tumor removal along with an outer cuff of normal tissue ("margin") in one intact specimen.<sup>11</sup> En bloc resection is shown to improve survival and prognoses of patients diagnosed with aggressive primary osseous tumors of the spine and some isolated metastases.<sup>26–30</sup> Furthermore, when functional tumors are located in other more anatomically accessible areas of the body (i.e., the abdominal cavity), en bloc resection is the preferred treatment option to optimize the clinical outcomes. For instance, in the treatment of adrenocortical tumors, en bloc resection of locally invaded organs in combination with regional lymphadenectomy and possible extraction of tumor thrombus from associated vascular structures (inferior vena cava, renal vein, etc.), if safe, is recommended.<sup>31,32</sup> Similarly, carcinoid tumors demonstrate good outcomes with en bloc resection in comparison with intralesional resection.<sup>33,34</sup> For other tumor subtypes located in more anatomically accessible areas, the clinical sequelae from the secretory molecule can be medically managed but en bloc resection demonstrates better rates of local control than intralesional resection.<sup>35</sup>

Functional secretory tumors that are metastatic to the spine are rare, and the difficulty in performing an en bloc resection of a portion of the spinal column usually precludes the treatment of this disease to highly experienced centers. In the limited reports available, en bloc resection appears to be a potential surgical option for functionally active spinal metastasis able to control the tumor-induced sequelae and offer potential long-term local tumor control.<sup>15,18,22,24</sup> Although an analysis of the local recurrence and/or long-term survival cannot be estimated based on the rarity of these tumor subtypes, one could hypothesize that in the absence of effective adjuvant treatment, intralesional resections have the potential to lead to increased local recurrence when compared with en bloc resection for any functional secretory spinal metastasis. Intralesional resections could potentially spill tumor into the resection cavity, leaving behind secretory tumor. Although this debulking may serve to decompress the spinal cord, any potential for a surgical cure may be lost depending on the tumor subtype. Some authors contend that functionally active secretory spinal metastases should thus be treated similar to primary osseous tumors when surgical intervention is indicated, so that the patient will have the best chance of a favorable outcome.<sup>15,22,36</sup> En bloc resection

**Table 1** Cases of en bloc resection of functional secretory spinal metastases

Author	Histology	Location	Synopsis	Adjuvant treatment	Treatment	Outcome
Naito et al 2009 <sup>53</sup>	Choriocarcinoma	L2	38-y-old woman with abnormal uterine bleeding and high serum levels of human chorionic gonadotrophin	Poor response to chemotherapy with methotrexate	Two-stage en bloc spondylectomy with embolization prior to second stage	Local recurrence, epidural metastasis, and death secondary to metastatic tumor progression
Sciubba et al 2009 <sup>15</sup>	Fibroblast growth factor 23-secreting phosphaturic mesenchymal tumor	T8	56-y-old woman with tumor-induced osteomalacia	None	En bloc T8 spondylectomy with expandable cage and T5-T11 fusion	Resolution of tumor-induced osteomalacia
Narayanan et al 2013 <sup>24</sup>	Carcinoid tumor	C7-T1	50-year-old woman with 4-mo history of numbness and mild left hand weakness	None	C7 corpectomy, en bloc resection of the tumor, and anterior C6-T1 fusion	No evidence of recurrence at 6-y follow-up
Kaloostian et al 2013 <sup>22</sup>	Pheochromocytoma	T10	23-y-old man with prior adrenalectomy presenting with focal thoracic pain	Prior chemotherapy and radiation	Angiographic embolization followed by single-stage posterior en bloc vertebrectomy with placement of cage, posterior instrumentation, and fusion	Symptom-free and no antihypertensive medication
Kaloostian et al 2014 <sup>19</sup>	Pheochromocytoma	L3-L4	28-y-old man with abdominal and low back pain	Prior chemotherapy and zoledronic acid and vertebroplasty	Angiographic embolization followed by two-stage en bloc vertebrectomy with placement of cage, posterior instrumentation, and fusion	No evidence of recurrence, symptom-free and neurologically intact at 21 mo



could potentially offer better rates of local recurrence and/or progression-free survival; however, further studies are needed to determine whether this statement holds true.

Unfortunately, there is considerable difficulty in making any generalizations or formulating any specific conclusions because of the paucity of publications in this subject area, particularly from a limited number of centers. Also, the variations in the age of these subjects make it difficult to ascertain their relevance in light of the improvements in standardization of spinal instrumentation and, more importantly, improvements in adjuvant chemotherapy and radiotherapy techniques. A comparison of the intraoperative and perioperative complications, as well as local tumor control, in both intralesional and en bloc resection would require more uniform reporting of outcomes to draw any formidable conclusions.

The morbidity associated with en bloc resection is increased compared with intralesional resection.<sup>27</sup> En bloc resections are technically demanding procedures with an estimated complication rate of 0.86 events per 100 patient-years reported in some series.<sup>27</sup> The complications associated with en bloc resection include local recurrence, hardware failures, wound dehiscence, hematomas, aortic dissection, and death. En bloc resections are associated with significant morbidity and loss of quality of life for patients who undergo this surgical approach. Thus, the decision to subject a patient to the risks of en bloc resection should be taken with great care as ~42% of patients can experience complications ranging from major to minor.<sup>37,38</sup> According to the McDonnell classification, major complications can include pulmonary embolism, pneumothorax, respiratory failure requiring tracheostomy, infection, hardware failure, paraplegia, hematomas, myocardial infarction, aortic or other vascular lesions, deep venous thrombosis, bowel injury, and death. Minor complications include superficial wound necroses, durotomies, pseudomeningocele, minor vascular lesions, peritoneal lesions, hematomas, retrograde ejaculation, kyphoscoliosis, respiratory failure, or reactive pleurisy. Higher rates of complication are associated with patients with tumor recurrence following intralesional excision, or contamination of the epidural space or a major body cavity (50% in some series).<sup>27,38</sup> The benefits and risks of en bloc resection to an individual patient must be weighed when surgical intervention is indicated and dictate that the operating surgeon have an understanding of various tumor subtypes and their associated pathophysiological properties. Either way, it is the spinal surgeon's duty to inform the patients of the potential options and provide guidance as to the benefits and risks of each approach, so that the patient may ultimately decide the best treatment option for them. Despite the inherent risks of en bloc resection, the potential benefit of a surgical cure may be more paramount than any of the associated morbidity to an individual patient.

## Conclusion

En bloc resection may be considered as a potential surgical option for the treatment of patients diagnosed with functional secretory hypermetabolic tumors. Although functional

secretory spinal metastases are rare, en bloc resection could potentially have better local recurrence rates and progression-free survival than traditional surgical methods.

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