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Extraneural Glioblastoma Multiforme Vertebral Metastasis

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Abstract

Glioblastoma multiforme (GBM) is the most common malignant central nervous system tumor; however, extraneural metastasis is uncommon. Of those that metastasize extraneurally, metastases to the vertebral bodies represent a significant proportion. We present a review of 28 cases from the published literature of GBM metastasis to the vertebra. The mean age at presentation was 38.4 years with an average overall survival of 26 months. Patients were either asymptomatic with metastasis discovered at autopsy or presented with varying degrees of pain, weakness of the extremities, or other neurologic deficits. Of the cases that included the time to spinal metastasis, the average time was 26.4 months with a reported survival of 10 months after diagnosis of vertebral metastasis. A significant number of patients had no treatments for their spinal metastasis, although the intracranial lesions were treated extensively with surgery and/or adjuvant therapy. With increasing incremental gains in the survival of patients with GBM, clinicians will encounter patients with extracranial metastasis. As such, this review presents timely information concerning the presentation and outcomes of patients with vertebral metastasis.

Keywords

Extracranial; Extraneural; Glioblastoma; Glioma; Metastasis; Spinal; Vertebral

BACKGROUND

Glioblastoma multiforme (GBM) is the most common malignant central nervous system (CNS) tumor, comprising approximately 15% of all primary brain tumors and approximately 45% of primary malignant brain tumors.¹ Historically, GBMs were not believed to metastasize outside of the CNS because of the presence of the blood–brain barrier and overall low median survival; however, several reports of extraneural GBM metastases have

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been reported.^{2,3} With improvements in the standard of care treatment of primary glioblastoma, including surgery, chemotherapy, and radiation, the incidence of extraneural metastases has increased exponentially. Lun et al. reviewed 88 cases of extracranial GBM metastases published between 1928 and 2009 and found that the time from diagnosis of GBM to detection of extracranial metastases was 8.5 months and from time of metastasis to mortality was 1.5 months.^{2,4–7} They also showed a progressive increase in time from detection of extracranial metastases to death at a rate of 0.7 months per decade (from 1949 to 2009), paralleling incremental advancements in diagnosis and treatment options for patients with glioblastoma.¹

Although the mechanism of extraneural spread of malignant gliomas remains unclear, several hypotheses have been proposed. Direct access via dural vessels to extrameningeal tissue is considered the most likely path in the development of extraneural metastases⁸ that is potentially initiated by surgical intervention. Evidence supporting this mechanism of metastatic spread is based on the pattern of seeding in the lungs and lymph nodes, which are the most frequent organs affected, suggesting either hematologic or lymphatic routes. Cases of metastasis in the absence of surgical intervention, radiation, or long survival after the onset of clinical symptoms make up a distinct minority of extracranial metastasis cases.^{9,10} These cases suggest other potential pathways of extracranial GBM spread via direct invasion through the dura mater and bone and cellular migration via ventricular drainage tubes.^{11,12} Circulating tumor cells recently have been found in the blood of 20%–39% of patients with GBM, supporting this mechanism.^{7,13} These new findings indicate that these tumor cells have the potential to extravasate through the blood–brain barrier and subsequently survive in the bloodstream through evasion of the immune system.^{14,15} As such, tumor seeding in the skeletal system could occur through hematogenous spread of these cells. Diffusion of the disease also could be postulated to occur secondary to vascular invasion induced by regional radiation therapy.^{16–18} An increased understanding of the molecular mechanisms underlying circulating tumor cell–specific properties, including epigenetic and posttranslational modifications, and factors or phenotypes allowing the extravasation from the primary site and survival in the circulatory system may allow for improved therapies and/or detection methods.^{5–7}

The characteristic nature of these tumors not to metastasize has been a subject of debate. Of greatest importance are the distinctly limited survival times for patients with glial tumors, which do not allow sufficient time for the metastatic tissue to grow to symptomatic proportions. Other explanations include the absence of lymphatics linking the CNS with the rest of the body,^{19–21} the ability of dense dural tissue to retard neoplastic invasion,^{22,23} the thin-walled nature of small cerebral veins, which may collapse before advancing tumor, and the failure of survival of neoplastic neuroglial cells in foreign territories.²¹ Nevertheless, glial tissue has demonstrated that it can survive outside of the CNS via inadvertent implantation at the time of surgery or through allogeneic organ transplants.²⁴ The ability of glial tissue to survive extraneurally depends primarily on the immunological properties of the host tissue.

We present a review of extraneural metastasis of glioblastoma to the bony vertebral column, excluding intradural or intramedullary spinal cord tumors. Relatively early diagnosis of

glioblastoma metastases to the vertebrae may significantly influence patients' status and medical treatment.

EPIDEMIOLOGY

Extraneural metastases from brain tumors most frequently are diagnosed late in the course of the disease, after a median of 2 years and in only 0.2% of all patients with glioblastoma.^{8,25} The presence of extraneural metastases is defined by criteria set forth by Weiss et al.²⁶, which include: 1) the metastatic lesion must have the same histologic characteristics of the CNS neoplasm; 2) the clinical course suggests that the first symptoms were caused by the CNS lesion; 3) a complete autopsy must have been performed and reported in sufficient detail to rule out the possibility of any other primary site; and 4) the morphology of the tumor of the CNS and of the distant metastases must have been identical with due allowance for differences in degrees of anaplasia.²⁴ In patients diagnosed with glioblastoma, the organs affected by extraneural metastases include the pleura and/or lung (60%), lymph nodes (51%), bones (31%), and liver (22%).⁸ Of the cases of skeletal metastases, the vertebral spine (73%), ribs (23%), sternum (18%), skull (14%), and acetabulum (9%) are the most common sites for GBMs to metastasize^{18,27} (Figure 1). The average age of patients who present with any extraneural metastases is 40 years.²⁸ Table 1 and Supplementary Table 1 summarizes the demographics and outcomes of published cases.

Of the 28 published cases of histologically diagnosed vertebral body GBM extraneural metastases, the male/female ratio was 19:9. The mean age of 38.4 years (range, 11–63 years) is much younger than the average age of initial presentation for patients newly diagnosed with a cerebral glioblastoma (54 years).²⁸ Further, the mean overall survival of the cases in our review with vertebral metastasis is approximately 26 months (range, 1–96 months) after their first diagnosis of glioblastoma. Of the 12 cases that reported on the survival of patients after diagnosis of vertebral metastasis, the average length of time from diagnosis of spinal metastasis to death was 10 months (range, 25 days to 48 months) (Figure 2). The average time to spinal metastasis, as reported for 10 cases, was 26.4 months (range, 4–90 months). Thirty-two percent of metastases localized to the thoracic spine, 28.6% to more than 1 spinal level, 17.9% to the lumbar spine, and 10.7% to the cervical spine. A significant number, 64.2%, of patients underwent surgery with adjuvant therapy (radiation, chemotherapy, or both) for the intracranial tumor, whereas 57.1% of the patients either underwent no treatment for the spinal metastasis or no course of treatment was noted.

Although the explanation is unclear, the younger age of presentation for patients with extraneural GBM metastases may be the cause of better overall survival of this patient population, relative to the older patient cohort, or conversely as the result of genetic differences in the primary GBM that could have a greater propensity to metastasize.²⁹ Previous neurosurgical intervention and prolonged postoperative survival seem to be the most important factors associated with extraneural metastasis, especially for those to the vertebrae.³⁰

Glioblastomas that metastasize to the vertebrae generally are supratentorial, and equally likely to occur in the right or left hemispheres. Although surgery is not necessary for

vertebral metastasis to occur, the vast majority of cases involve a previous craniotomy during which only debulking or subtotal resection of the tumor was achieved. In all cases with surgical intervention, a combined course of radiation at levels between 5000 and 7000 cGy and chemotherapy was given in the postoperative period.^{8,9,22,24,28,31–38} The most commonly employed chemotherapy agents included temozolomide, bis-chloroethylnitrosourea, and nimustine hydrochloride.^{31,34,38,39}

Glioblastoma rarely metastasizes to the vertebral column alone. In all reported cases except one, glioblastoma metastasis to the vertebral body is accompanied by GBM metastasis to other locations in the body. The frequency of metastatic involvement of other organ systems follows the overall frequencies of extraneural metastasis of GBM, i.e., lung, followed by lymph nodes, other bony sites, and liver.

In the spinal column, metastases are most common to thoracic vertebrae, followed by the lumbar, cervical, and sacral regions.^{12,18} Thoracic metastases may be the result of hematogenous or lymphatic spread, potentially after tumor invasion in the lungs. Metastases to the lumbar vertebrae may be the result of hematogenous spread, whereby glioblastoma cells enter Batson's plexus, which are a network of valveless veins that connect the deep pelvic veins with the internal vertebral plexus and lead to tumor seeding in the lumbar and sacral vertebrae.¹² Consistent with this hypothesis, isolated GBM metastases to the cervical vertebrae are relatively rare compared with the reports of multiple metastases of GBM to the lumbar and sacral vertebrae. In other cases, vertebral body tumors have been found in isolation even in the same patient, suggesting that metastatic involvement of the spinal neuraxis may occur in multiple ways.

CLINICAL PRESENTATION

In more than half of the cases, GBM metastases to the vertebral body are clinically silent and the lesions are discovered during imaging or at autopsy.^{9,22,30,39–42} Of symptomatic cases, patients with vertebral body metastases from glioblastoma most commonly present with acute or insidious pain in the region of the axial skeleton involved by tumor and often are accompanied by varying degree of progressive paresis.^{28,34,35,37} Patients also report diffuse back pain, or diffuse discomfort and stiffness, not relieved by analgesics.^{20,23,28,31–33,38} Weakening of the vertebrae as the result of metastatic infiltration also can lead to segmental instability, pathologic fracture,³¹ or kyphotic deformity, leading to increased pain and/or neurologic deficit. Axial pain can occur with or without hypesthesia, radicular pain, or other peripheral neurologic symptoms.⁹ Other symptoms include weight loss, bladder/bowel dysfunction, and/or weakness/paralysis.^{8,28} These symptoms generally worsen as the disease progresses. In some cases, significant laboratory findings include hypercalcemia, high creatinine, high white blood cell count, and high nitrogen.³⁹

HISTOLOGIC FEATURES

Interestingly, spinal column metastases have rarely demonstrated the characteristic pseudopalisading of glioblastoma that is present in the primary tumor and in other

extraneural metastatic sites (e.g., lung, liver).²² The histopathology of GBM vertebral body metastasis can sometimes consist of both glial and sarcomatous components³² with marked desmoplasia.²² On macroscopic examination after autopsy, metastatic tumors in the vertebra are described as round and white or tan colored, roughly 0.5–3.0 cm in diameter. Less often, GBM metastases diffusely infiltrate vertebra and are only discovered through radiologic imaging. Immunohistochemical staining of vertebral body GBM metastases with glial fibrillary acidic protein is a sensitive and specific marker for glial-derived tumors and is useful in confirming the tumor's glial origin. Markedly anaplastic tumors may be negative, however, because the sample size is often too small and glial fibrillary acidic protein expression, if present, may be so only in a subpopulation of tumor cells.²⁸

IMAGING

Early radiologic detection and treatment may not significantly prolong survival but may improve a patient's quality of life. For patients with GBM metastases, the findings can either be discovered in a symptomatic patient who underwent subsequent imaging, or incidentally on a routine surveillance bone scan. The bone involvement seen with GBM can be osteolytic,^{23,24} osteoblastic,^{16,36} or mixed on plain radiographs and computed tomography imaging. Both magnetic resonance imaging (MRI) with gadolinium as well as Tc-99m single-photon emission computed tomography bone scans are sensitive to detect vertebral body metastases from GBM.⁸ MRI and bone scans are complementary, because MRI will pick up osteoblastic and osteoclastic activity and has greater sensitivity for detecting vertebral metastasis because of direct visualization of the tumor and spinal cord or nerve roots, whereas, bone scans provide a larger area of coverage.

On MRI, vertebral body metastases are hypointense on T1-weighted imaging, heterogeneously hyperintense on T2-weighted imaging, partially contrast enhancing, and may demonstrate ring enhancement.²⁰ Vertebral bodies infiltrated with tumor are irregularly hyperdense compared with normal vertebrae. Computed tomography myelography has been used successfully; however, this modality is an invasive procedure that requires the injection of iodinated contrast material,³⁵ and as such has associated risks. On bone scan, vertebral lesions generally are accompanied by other lesions in the long bones or pelvis and often in conjunction with evidence of diffuse marrow involvement. In several cases, the marrow involvement was so widespread it resulted in diffusely increased uptake throughout the entire skeleton.⁸ The resultant bone scan lacked specific "hot spots" and could easily have been interpreted as normal, although vertebral metastases were radiologically apparent in these patients.³⁵

TREATMENT AND PROGNOSIS

The reported mean survival from time of first craniotomy in patients with metastases of any sort from glial tumors was 18 months.³⁰ In our review of the 28 patients in the literature with vertebral body metastases, we found the mean survival time to be approximately 26 months (range, 1–96 months) after the first diagnosis of glioblastoma. Of the 12 cases that reported on the survival of patients after diagnosis of vertebral metastasis, the average length of time before death was 10 months (range, 25 days to 48 months). Given that the average survival

after diagnosis of vertebral metastasis is 10 months, surgical management should be reserved for patients with gross spinal instability or potentially reversible compressive myelopathy with the goal of preserving quality of life. Even with these indications careful consideration of the risks and benefits of surgical intervention should be made with the patient given the short life expectancy. These patients may benefit from decompression and/or fusion as these interventions can provide spine stability and pain control. Some authors have reported increased patient mobilization and improved quality of life after palliative resection of vertebral body metastases. In the majority of cases, both radiation and chemotherapy are applied in a palliative intention, with or without surgery. Cobalt therapy is shown to provide good pain relief in 1 patient suffering from back pain secondary to GBM vertebral body metastases.²³ Bevacizumab, an inhibitor of vascular endothelial growth factor that normalizes tumor vasculature and is approved for the treatment of GBM, has demonstrated some benefit for patients diagnosed with glioblastoma; however, its role in tumor progression and metastatic dissemination remain unclear.^{4,5,43,44}

FURTHER RECOMMENDATIONS

Patients with glioblastoma are experiencing longer survival as the result of advances in diagnostic tools, surgical resection, radiation therapy techniques, and integration of chemotherapy and targeted therapies. This trend is expected to continue with this increased survival; the incidence of symptomatic metastasis to the vertebral column is expected to increase.^{2,12} Patients complaining of bone pain or back pain, or patients presenting with anemia, thrombocytopenia, hypercalcemia, or pseudohyperparathyroidism, should be evaluated for extraneural metastasis with computed tomography, MRI or bone scanning.³⁹ Because false-negative results have been reported, repeat studies should be considered if the patient's complaints persists, with attention towards both the presumed metastatic site and the site of primary tumor as an explanation for the symptoms.³¹ Intervention should be reserved for those cases demonstrating gross spinal instability and/or spinal cord compression leading to neurologic deficit. Although these indications may be apparent, the surgeon should outline the risks and benefits of surgical intervention in the context of risks and benefits of intervention, life expectancy, and informed decision-making.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

CNS	Central nervous system
GBM	Glioblastoma multiforme
MRI	Magnetic resonance imaging

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Figure 1.

Graph depicting frequency of bone metastasis from glioblastoma multiforme (GBM) based on Pasquier et al.'s¹⁸ series of extracranial metastasis of GBM.

Figure 2.
Survival of patients diagnosed with a glioblastoma multiforme (GBM) spinal metastasis from (A) primary GBM diagnosis and (B) diagnosis of GBM spinal metastasis.

Table 1

Demographics and Outcomes of GBM Metastases to the Vertebral Column

Total No. Patients with Spine Metastases		Glioblastoma (N = 28)
Sex, male, <i>n</i> (%)		19 (67.9)
Age at primary, years (range)		38.4 (11–63)
Mean time to spine metastasis, months (range) *		26.4 (4–90)
Location, <i>n</i> (%)		
Cervical		3 (10.7)
Thoracic		9 (32.1)
Lumbar		5 (17.9)
Multilevel		8 (28.6)
Unknown		3 (10.7)
Treatment of primary GBM, <i>n</i> (%)		
Surgery alone		5 (17.9)
Radiotherapy and/or chemotherapy		1 (3.6)
Surgery and adjuvant therapy		18 (64.2)
No treatment/unknown		4 (14.3)
Treatment of spinal metastasis, <i>n</i> (%)		
Surgery alone		0 (0)
Radiotherapy and/or chemotherapy		3 (10.7)
Surgery and adjuvant therapy		9 (32.1)
No treatment/unknown		16 (57.1)
Survival, <i>n</i> (%)		
Patients with known survival		25 (89.3)
Patients with unknown survival		3 (10.7)
<3 months survival		1 (4)
3–11 months survival		6 (24)
12–23 months survival		11 (44)
24–60 months survival		4 (16)
>60 months survival		3 (12)
Overall mean survival from spine metastasis diagnosis, months, (range)		10 (25 days–48 months)

All percentages based off of a total # of patients (*n*), except for survival where percentages are based off of patients with known survival

GBM, glioblastoma multiforme.

* Time to spine metastasis was not reported in 18 studies.