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Leptomeningeal spinal metastases from glioblastoma multiforme: treatment and management of an uncommon manifestation of disease

A review

Cort D. Lawton, B.A.,[1] Daniel T. Nagasawa, M.D.,[2] Isaac Yang, M.D.,[2] Richard G. Fessler, M.D., Ph.D.,[1] and Zachary A. Smith, M.D.[1]

[1]Department of Neurological Surgery, Northwestern University, Chicago, Illinois; and [2]Department of Neurological Surgery, University of California, Los Angeles, California

Glioblastoma multiforme (GBM) is one of the most common and aggressive primary brain tumors, composing 12%–20% of all intracranial tumors in adults. Average life expectancy is merely 12–14 months following initial diagnosis. Patients with this neoplasm have one of the worst 5-year survival rates among all cancers despite aggressive multimodal treatment consisting of maximal tumor resection, radiation therapy, and adjuvant chemotherapy. With recent advancements in management strategies, there has been improvement in the overall trend in patient outcomes; however, recurrence remains nearly inevitable. While most tumors recur locally, metastases to distal locations have become more common. Specifically, the last decade has seen an increased incidence of spinal metastases, representing an emerging complication in patients with intracranial GBM. However, the literature regarding prevention strategies and the presentation of spinal metastases has remained scarce. As local control of primary lesions continues to improve, more cases of spinal metastases are likely to be seen. In this review the authors present a new case of metastatic GBM to the L-5 nerve root, and they summarize previous cases of intracranial GBM with leptomeningeal spinal metastatic disease. They also characterize key features of this disease presentation and discuss areas of future investigation necessary for enhanced prevention and treatment of this complication.
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Key Words • **glioblastoma multiforme** • **spinal metastasis** • **metastasis** • **oncology**

Glioblastoma multiforme is one of the most common and aggressive primary brain tumors in adults, composing 12%–20% of all intracranial tumors and more than 50% of glial neoplasms.[70] It has a reported incidence of 2–3 cases per 100,000 individuals per year in Europe and North America, and patients typically present after the 6th decade of life.[70] These tumors are less common in children, accounting for only 7%–9% of all pediatric intracranial lesions.[14] Patient management has remained challenging given the tumor's high proliferation rate and extensive invasion throughout normal brain tissue, both of which lead to a mean survival of 12–14 months after an initial diagnosis.[22,25,43,54,56] This neoplasm is associated with an extremely poor prognosis and one of the worst 5-year survival rates among all human cancers, with nearly inevitable tumor recurrence. Although as many as 90% of these lesions recur intracranially,[34,47,56] the last decade has seen both prolonged survival rates and escalating reports of distal CNS recurrences. While systemic metastasis to extracranial sites is extremely rare,[27,32,33,35] spinal cord metastases have been reported with increased frequency.[16,35,65]

Maximal resection is the initial therapy of choice for intracranial GBM, frequently leading to rapid improvement of symptoms and associated with prolonged survival.[35,61,70] Recent technological advancements have allowed better planning and execution of neurosurgical procedures. Multimodal imaging, including conventional and functional MRI and diffusion tensor imaging se-

Abbreviation used in this paper: GBM = glioblastoma multiforme.

quences to visualize eloquent brain areas and fiber tracts, are routinely used for surgical intervention to decrease morbidity and mortality.[61] Additionally, 5-aminolevulinic acid fluorescence–guided neurosurgery has demonstrated more complete tumor resection, resulting in improved 6-month progression-free survival rates.[71] Furthermore, intraoperative monitoring and cortical and subcortical stimulation aid in reducing the risk of permanent disability from tumor resection.[63]

Advances in radiation therapy and chemotherapy have significantly improved mean survival rates as well. Postoperative external radiation therapy, at a minimum total dose of 54 Gy, has been shown to improve mean survival from 4–5 to 9–12 months.[21,28,44,70] Investigators for the European Organization for Research and Treatment of Cancer and the National Cancer Institute of Canada found similar results in a randomized Phase III trial on 573 patients.[72,73]

Despite these advances, all patients eventually experience tumor recurrence. Approximately 80%–90% of all GBM recurrences are local to the site of original tumor burden, that is, > 80% of lesions arise within 2 cm of the original tumor border.[34,47,56] However, metastases to more distal sites have become increasingly prevalent because of longer survival rates.[8,52,56,73] Extracranial extraspinal metastases are extremely rare, occurring at an estimated incidence of less than 2%.[27,32,33,35,37] In these cases, metastases have been observed mainly in the lung, liver, lymph nodes, bone, and viscera. In the absence of a previous craniotomy, one mechanism of extracranial metastasis involves invasion of the dural veins or sinuses.[3] Primary spinal cord tumors have also been reported to metastasize to intracranial sites as well.[15,18,40,50] The most common sites of metastasis include the subarachnoid space, ventricles, cerebellum, hypothalamus, brainstem, thalamus, and septum pellucidum.[50]

The rate of spinal metastasis from intracranial GBM has been variably reported to be 0.4%–2.0% of patients.[16,35,65,70,77] Despite the limited number of well-documented cases, there has been an increase in the frequency of spinal cord involvement in recent years.

In this review, we discuss the development of clinically significant spinal cord metastases from primary GBM. This clinical presentation, although still rare, has been reported more frequently in the last decade. Given the scarce literature on effective treatment options, we address the current management of metastatic spinal cord disease and discuss areas for improvement in what has become a more common complication in patients with GBM.

Methods

A single investigator (C.D.L.) systematically selected specific reports written between 1980 and 2012. The key terms "GBM" and "spine," as well as "glioblastoma" and "spine metastases," were used to generate a broad selection of papers from both the PubMed and PubMed Central databases. The search generated 87 reports. We eliminated any non-English reports as well as any reports pertaining to primary malignancy in the spine, those on manifestations of the disease primarily located in the spinal column (including vertebral body disease), and those failing to present new cases or aspects of this particular presentation. Twenty-three separate reports were culled from this search, as well as a detailed review of the literature discussed in more recent case reports and series. In these 23 reports, 42 separate cases were described; treatment and outcome data were available in 35 of these cases (Table 1).[1,2,5,7,10,11,13,20,26,32,35,36,38,39,46,48,58,60,66,68,70,74,77] From these cases we quantitatively evaluated the presentation trends, as reported in the text and associated tables.

Results

Spinal Metastasis of GBM

Our analysis of presentation trends included data from all 42 documented cases of intracranial GBM with spinal metastatic lesions. Patients had a mean age of 43 years and an average survival of 17 months from the initial intracranial diagnosis. Historically, GBM metastases to the spinal cord have most commonly occurred in the lower thoracic, upper lumbar, and lumbosacral regions (Fig. 1).[46,57] Additionally, nerve roots of the cauda equina, nerve root sleeves, and fundus of the thecal sac have been other sites of metastasis (Fig. 2),[46] with rare intramedullary and entire spinal cord involvement.[77] We found 13 metastases (31%) to the cervical region, 22 (52%) to the thoracic region, 17 (40%) to the lumbar region, and 3 (7%) to the cauda equina/conus medullaris (Table 2).

Reports of spinal metastases remain scarce in the literature, in part because most patients with GBM do not live long enough for small tumor implants to grow to symptomatic size. Furthermore, surveillance imaging of the spine is often not undertaken. Accordingly, postmortem observations of spinal seeding have been found to be much higher than the incidence of clinically symptomatic metastasis. Autopsy studies in which patients had no signs or symptoms of spinal metastasis have been documented, with rates of postmortem CSF spread ranging from 20% to 60%, with variation based on the original location of the primary tumor.[9,24,57,62,78] Firsching et al.[29] suggested that leptomeningeal dissemination in patients occurs when primary tumor invades the CSF circulation. Supratentorial GBM lesions have demonstrated CSF infiltration in approximately 15%–25% of autopsy studies.[4,24,62]

Increased CSF dissemination is associated with poorly differentiated intracranial tumors with a greater amount of necrosis, and yet leptomeningeal spread can be seen with all degrees of differentiation.[30] While the incidence of symptomatic metastases traditionally has been low, recent years have shown a steady increase in this rate. In one study involving 600 patients, 2% of them had symptomatic CSF tumor dissemination from an intracranial lesion.[77] However, this relatively lower incidence of clinical manifestation as compared with the incidence of CSF seeding suggests that dissemination occurs in the end stages of the disease, with most patients not surviving long enough for symptomatic spinal metastasis to develop. In support of this notion, our analysis revealed an average interval of 13 months between the diagnosis of primary intracranial GBM and spinal metastatic disease (Table 3), a latency period that parallels the median survival for most patients aggressively treated for an intracranial lesion.[25,43,56,77]

TABLE 1: Literature summary of spinal metastases of intracranial GBM: 42 cases*

Authors & Year	Sex	Age (yrs)	Location of Primary Tumor	Primary Treatment	Site of Metastasis	Interval From Primary Dx to Metastasis (mos)	Clinical Symptom	Metastasis Treatment	Interval From Metastasis to Death (mos)	Interval From Primary Dx to Death (mos)
Ammerman et al., 2011	M	50	temporal & parietal lobe	resection, XRT, TMZ	leptomeningeal masses C3–5	5	paralysis	supportive care	0†	5
Birbilis et al., 2010	F	57	pineal area	biopsy, XRT, chemo	intramedullary lesion at C7–T3	37	NS	biopsy	2	39
Shah et al., 2010	M	51	temporal lobe	resection, XRT, TMZ	lower dorsal & lumbar spine	1.5	pain, paresis, bladder-bowel dysfunction	spinal XRT	1	2.5
	M	22	posterior frontal lobe	resection, XRT, TMZ	dorsal & dorsolumbar anterior subarachnoid space	3	pain	none	1‡	3.25
Scoccianti et al., 2008	NS	NS	NS	NS	intramedullary	13	NS	XRT (30 Gy)	4	17
Arzbaecher, 2007	F	63	temporal lobe	resection, XRT, TMZ	T3–11	12	paralysis, sensory loss, bowel dysfunction	T5–6 laminectomy, biopsy, XRT, chemo	4	16
Karaca et al., 2006	M	67	temporal lobe	resection, XRT	intramedullary T11–L1	2	paresis, pain	XRT (21 Gy), chemo (CCNU)	4	6
	F	20	frontal lobe	resection, XRT	lower thoracic, upper lumbar region, cauda equina	12	pain	XRT (39 Gy)	6	18
	F	28	frontal & parietal lobe	resection, XRT, TMZ	intradural extramedullary T-6, T-8, T-9, T12–L1	17	paresis	spinal XRT (49 Gy)	3	20
Stark et al., 2005	NS	NS	NS	NS	NS	5	NS	NS	NS	NS
	NS	NS	NS	NS	NS	8	NS	NS	NS	NS
	NS	NS	NS	NS	NS	11	NS	NS	NS	NS
Toledano Delgado et al., 2006	M	65	temporal lobe	NS	multiple intradural extramedullary spinal metastases	10	pain, paresis, sensory loss	NS	2	12
Fakhrai et al., 2004	F	50	mesotemporal area	NS	entire spinal cord	NS	pain	XRT	3	NS
	M	39	mesotemporal area	NS	multiple spinal seeding	NS	bladder dysfunction, paresis	XRT to C3–7, chemo	3	NS
Kanai et al., 2005	F	4	pons, midbrain	NS	intraspinal leptomeningeal dissemination	NS	pain	NS	4	NS
Pohar et al., 2004	F	63	posterior parietal lobe	NS	intramedullary tumor at C2–3, C5–7, T-1, focal intradural mass at T7–8	NS	sensory loss	craniospinal XRT	3	NS

(continued)

TABLE 1: Literature summary of spinal metastases of intracranial GBM: 42 cases* *(continued)*

Authors & Year	Sex	Age (yrs)	Location of Primary Tumor	Primary Treatment	Site of Metastasis	Interval From Primary Dx to Metastasis (mos)	Clinical Symptom	Metastasis Treatment	Interval From Metastasis to Death (mos)	Interval From Primary Dx to Death (mos)
Jahraus et al., 2003	F	6	pons w/ extension into thalamus & medulla	NS	T6–8	NS	pain, paresis	laminectomy, duraplasty, biopsy, XRT, chemo	5†	NS
Lindsay et al., 2002	M	42	splenium & posterior parietal lobe	biopsy, XRT	T-3 & lower thecal sac	24	pain, paresis	XRT to lumbar spine (8 Gy) & chemo (CCNU)	12	36
Alatakis et al., 2001	M	55	temporal lobe	resection, XRT, TMZ, BCNU	intradural extramedullary mass at T8–10	18	pain, sensory loss	XRT (20 Gy) to thoracic spine	3	21
Chang et al., 2001	M	51	temporal lobe	resection, XRT	C4–5, T-12, L-2	31	pain	none	1	32
Hübner et al., 2001	F	46	frontobasal region	resection, XRT, chemo	intradural tumor at L-3	12	pain, sensory loss	chemo	9	21
	M	30	temporal lobe	resection, XRT	cauda equina & S-1 root	12	pain, sensory loss	craniospinal XRT (36 Gy)	6	18
	F	36	mesotemporal area	resection	C6–7, L4–S1, T-12	16	paresis, bladder dysfunction	resection	8	24
Buhl et al., 1998	M	59	frontal lobe	resection, XRT	conus medullaris & cauda equina (L4–5), intramedullary lesions at C-2, C-4, T-1	8	pain, sensory loss, paresis, bladder dysfunction	none	2	10
	F	64	temporal & parietal lobes	resection, XRT	T-2, T-4, T-7	5	sensory loss, paresis	none	2	7
Hamilton et al., 1993	NS	NS	NS	NS	intramedullary thoracic spinal cord	10	NS	NS	NS	NS
Lam et al., 1991	M	68	frontal lobe	NS	C3–T1	NS	pain, paresis, bladder dysfunction	XRT to cervical cord	2	NS

(continued)

TABLE 1: Literature summary of spinal metastases of intracranial GBM: 42 cases* *(continued)*

Authors & Year	Sex	Age (yrs)	Location of Primary Tumor	Primary Treatment	Site of Metastasis	Interval From Primary Dx to Metastasis (mos)	Clinical Symptom	Metastasis Treatment	Interval From Metastasis to Death (mos)	Interval From Primary Dx to Death (mos)
Vertosick & Selker, 1990	M	26	temporal & parietal lobes	NS	intradural extramedullary lower thoracic & lumbar	8	paresis, bladder dysfunction, pain	XRT (30 Gy)	1	9
	M	43	temporal & parietal lobes	NS	intradural extramedullary lower thoracic & lumbar	20	sensory loss, bladder dysfunction, pain	XRT (40 Gy)	2	22
	F	30	temporal & parietal lobes	NS	intradural extramedullary lumbar	4	sensory loss, paresis, pain, bladder dysfunction	XRT (30 Gy)	4	8
	M	61	temporal & parietal lobes	NS	intradural extramedullary cervical, thoracic, & lumbar	12	pain, paresis	spinal XRT	2	14
	F	21	frontal lobe	NS	intradural extramedullary thoracic	60	pain, paresis	decompressive laminectomy & spinal XRT (25 Gy)	2	62
	M	18	parietal lobe	NS	intramedullary cervical	9	pain, paresis	XRT	2	11
	F	47	frontal & temporal lobes	NS	intradural extramedullary lumbar	10	pain	XRT	7	10
	F	43	temporal & parietal lobes	NS	intramedullary thoracic	15	pain, paresis	XRT	3	10
	M	47	temporal & parietal lobes	NS	intradural extramedullary lumbar	7	pain, paresis, bladder dysfunction	XRT (40 Gy)	3	10
	F	52	temporal & parietal lobes	NS	intradural extramedullary thoracic	7	pain	XRT (40 Gy)	NS	NS
Onda et al., 1986	M	48	temporal lobe	NS	lesions below C-5	NS	paresis, sensory loss, bowel dysfunction	XRT to C1–T3	3	NS
	M	42	temporal & parietal lobes	NS	perispinal cord masses above C-6, extramedullary tumors at C-6 & C-7	NS	paralysis, sensory loss	C5–T1 laminectomy, XRT to C1–T8	12	NS
Bukeo et al., 1985	M	32	parietal & occipital lobes	NS	spinal epidural tumor	NS	pain, paralysis, bladder dysfunction	T10–L1 laminectomy, XRT	8	NS
Corbett & Newman, 1981	M	45	frontal lobe	NS	diffusely thickened spinal cord from T-3 extending caudally for 5 cm, roots of cauda equina	NS	pain, sensory loss	NS	3	NS

* BCNU = carmustine; CCNU = lomustine; chemo = chemotherapy; Dx = diagnosis; NS = not specified; TMZ = temozolomide; XRT = radiation therapy.
† Sudden cardiac arrest after 3 days.
‡ Value refers to number of weeks.

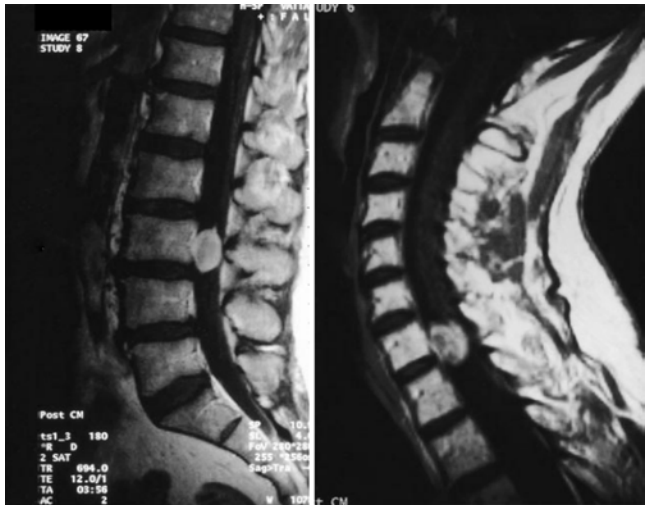

Fig. 1. Sagittal T1-weighted MR images demonstrating a contrast-enhanced lesion at L-3 **(left)** and C-6 **(right)**. Reproduced with permission from Hübner et al: *Acta Neurochir (Wien) 143:*25–29, 2001.

Regarding intracranial tumor location, the majority of primary GBMs tend to be located in the third and lateral ventricles, with involvement of the fourth ventricle being uncommon in cases of CSF tumor dissemination.[57] The mechanism for dissemination involves invasion of the basement membrane structures, with subependymal growth and invasion of the choroid plexus, resulting in metastatic spread along the CSF pathways.[30] Invasion of a primary tumor into the cortical surface can also lead to subpial spread, followed by leptomeningeal dissemination.[12,30] Once a tumor cell penetrates the perivascular space, it can move freely within the subarachnoid space.

Direct invasion of the ependyma, fissuring of the ependyma from hydrocephalus, and fragmentation of the tumor

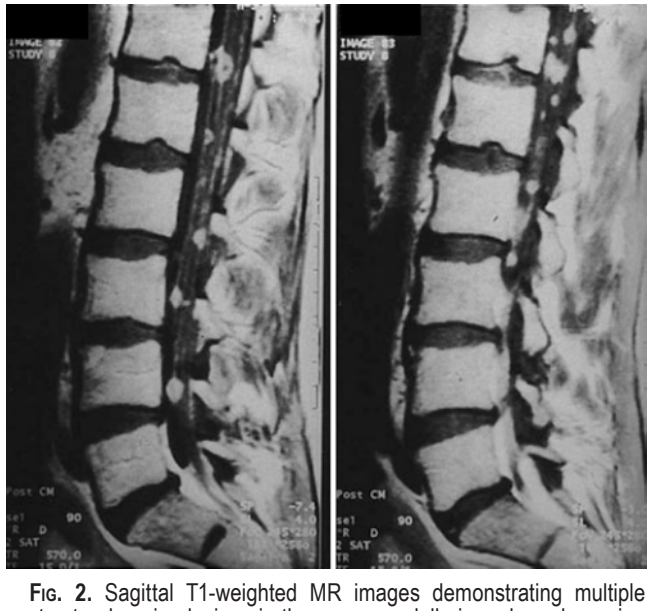

Fig. 2. Sagittal T1-weighted MR images demonstrating multiple contrast-enhancing lesions in the conus medullaris and cauda equina **(left)** and a more lateral view of these same lesions **(right)**. Reproduced with permission from Buhl et al: *Acta Neurochir (Wien) 140:*1001–1005, 1998.

TABLE 2: Location of spinal metastases from intracranial GBM in 39 patients

Location of Metastasis	No. of Cases (%)
cervical	13 (31.0)
thoracic	22 (52.4)
lumbar	17 (40.5)
cauda equina/conus medullaris	3 (7.1)

in contact with CSF are all risk factors for CSF tumor dissemination. Despite the microscopic spread of tumor cells resulting from GBM resection,[24,57] some argue that there is no evidence that this spread increases the risk of implantation and growth leading to metastatic disease.[31] In contrast, other authors believe that the possibility of tumor cell spread to the spine is increased during craniotomy.[23] Grabb at el.[31] suggested that a greater risk of CSF dissemination is associated with recraniotomy, probably from repeated manipulation, a more aggressive tumor type, and radiotherapeutic and chemotherapeutic depression of immune function. Furthermore, there have been numerous reports of postoperative and peritoneal metastases following the implantation of a ventriculoperitoneal shunt, demonstrating that metastatic disease can result from intraoperative manipulation and displacement of malignant cells into the blood, CSF, and lymph system.[37,51,55,65] However, intraoperative ventricular entry and proximity of the intracranial lesion to the ventricular system remain controversial factors in the increased risk of CSF dissemination.[23,31,57,62,77] In addition, cases of extracranial metastasis have been reported in the absence of craniotomy.[1,35]

TABLE 3: Patient demographics and survival analysis in patients with GBM

Parameter	No. (%)
sex	
M	21 (50)
F	16 (38)
unknown	5 (12)
age in yrs*	
mean	43
range	4–68
interval from primary diagnosis to spinal metastasis in mos†	
mean	13.3
range	1.5–60
interval from spinal metastasis to death in mos‡	
mean	3.7
range	0.1–12
interval from primary diagnosis to death in mos§	
mean	17.2
range	2.5–62

* Based on 37 patients.
† Based on 32 patients.
‡ Based on 37 patients.
§ Based on 27 patients.

Symptoms related to spinal metastatic dissemination are largely related to tumor localization and extent of disease. Common symptoms include radicular pain, myelopathy, sensory loss, gait disturbances, weakness, and pain in the lower back, interscapular area, and neck, followed by paraparesis, quadriparesis, paraplegia, bowel and/or bladder dysfunction, and sexual dysfunction.[10,20] In our analysis we found the following presentations (based on 36 patients for whom these data were available): pain (72%), paresis (53%), bowel and/or bladder dysfunction (33%), sensory loss (33%), and paralysis (11%; Table 4).

The reason for the increased number of reported spinal metastasis cases remains highly controversial. One factor that plays a significant role is imaging of the neuroaxis. Because metastatic deposits consist of a thin layer of tumor and lack vasogenic edema, technical problems involving volume averaging with CSF and excessive artifacts make noncontrast MRI ineffective.[42,77] The advantages of contrast MRI include the absence of bone-derived artifacts, good spinal cord–CSF–thecal sac contrast, multiplanar imaging capabilities, improved discrimination of intra- and extramedullary lesions, and lack of ionizing radiation.[6,10,46] Moreover, T1-weighted and intermediate T1- and T2-weighted pulse sequences allow optimal identification of metastatic deposits in the subarachnoid space. Metastatic GBMs typically present with high signal intensity on T2-weighted images and low signal intensity on T1-weighted images. However, given the relative brightness of CSF, metastatic lesions may be poorly defined in heavily T2-weighted pulse sequences.

While contrast MRI is the preferred diagnostic option, other imaging techniques may be useful in selected cases. For example, PET scanning for biopsy target selection provides enhanced tumor delineation and differentiation between residual lesion and posttherapeutic changes.[45] The introduction of open MRI, fluorescence, and neuronavigation has also contributed to the prolonged survival recently seen in patients with GBM.[35] These imaging techniques have improved early detection of spinal metastases, enhanced treatment evaluations, and assisted in maximizing tumor resection.

Prognosis and Treatment

Survival following spinal metastases of GBM remains invariably poor, with a fatal outcome always occurring.[70] Our analysis demonstrated an average interval of approximately 4 months from the diagnosis of a spinal metastatic lesion until death, giving the population a mean survival period of 17 months from the time of their primary diagnosis (Table 3). However, in rare cases involving younger patients, survival longer than 20 months has been seen after the diagnosis of a primary lesion.[35,48,77]

Despite the lack of consensus regarding optimal management of spinal cord metastases, several strategies with varying degrees of success have been documented. Possible treatment options have included external beam radiation therapy (25–60 Gy in 2.5-Gy fractions),[1,5,26,39,46,48,58,60] decompressive surgery (confirmation of diagnosis, pain management),[5,35,36,58,70] intravenous or intrathecal chemotherapy,[5,26,35,36,39,48] corticosteroids and opiates,[1] and prevention of CSF dissemination (stereotactic biopsy, cranial radiotherapy, and delayed tumor resection).[77] Radiotherapeutic treatment of the entire craniospinal axis has also been suggested.[60] In our analysis, 23 cases (66%) had treatment with radiation therapy alone and a mean survival of 6.2 months, 6 cases (17%) had no treatment and a mean survival of 8.7 months, 4 cases (11%) had both radiation therapy and chemotherapy and a mean survival of 5.6 months, 1 case (3%) had chemotherapy alone and a mean survival of 9 months, and 1 case (3%) had resection and a mean survival of 8 months (Table 5). While definitive conclusions cannot be reliably drawn because of the small sample sizes, there does not appear to be any obvious survival advantage of one therapy over another, indicating that treatment options may be best targeted toward symptomatic control. Nevertheless, radiation therapy was the most widely used intervention. In one of the longest surviving cases, Lindsay et al.[48] treated a patient with radiation therapy (1 dose at 8 Gy) and chemotherapy (3 cycles of lomustine), and the patient survived 12 months after the diagnosis of a thoracic spinal metastasis. Onda et al.[58] treated a patient with cervical metastasis using a laminectomy for decompression followed by radiation therapy, resulting in 12 months of survival after metastasis diagnosis. Note, however, that the true efficacy of these treatments remains unknown and has not been validated by studies with higher-class evidence.

Several large series have demonstrated excellent clinical outcomes following the resection of various spinal neoplasms.[19,49,67] And while the resection of spinal metastases may be beneficial for symptomatic relief, the optimal surgical management of malignant intramedullary spinal cord tumors remains controversial.[49,53] Resection for nondisseminated tumors has been associated with increased survival, although such an association has not been established for intramedullary tumors. Consequently, some authors argue that aggressive surgical management is unwarranted in spinal GBM.[64] For intramedullary GBM, extensive resection is often difficult because of ill-

TABLE 4: Summary of clinical presentations in 36 patients

Presenting Symptom	No. of Patients (%)
pain	26 (72.2)
paresis	19 (53)
bowel/bladder dysfunction	12 (33)
sensory loss	12 (33)
paralysis	4 (11)

TABLE 5: Survival outcomes in the treatment of spinal metastases in 35 patients

Treatment	No. of Cases (%)	Mean Survival After Metastasis (mos)
XRT only	23 (65.7)	6.2
no treatment	6 (17.1)	8.7
XRT & chemo	4 (11.4)	5.6
chemo only	1 (2.9)	9
resection	1 (2.9)	8

defined tumor margins from the spinal cord and adjacent tissues, with an overall poor prognosis regardless of the therapeutic intervention. Many institutions have resorted to diagnostic biopsy or limited resection followed by radiation and adjuvant chemotherapy given the risk of serious postoperative neurological complications. However, many authors argue for an aggressive approach via gross-total removal when possible.[59,76] Postoperative irradiation is generally recommended, especially in cases of partial resection, and has been shown to result in increased survival and neurological improvements.[17]

Intraoperative neurophysiological monitoring has made the goal of gross-total resection and microsurgical removal more feasible. Surgical decompression may allow improved pain control, palliation of symptoms, and diagnostic confirmation. Debulking of larger metastatic deposits offers an important adjunct to radiotherapy and chemotherapy, but in many cases the diffuse nature of GBM may not allow meaningful resection.

Although intravenous or intrathecal chemotherapy is more effective for extraneural metastasis,[69] its advantages for intramedullary metastasis have not been proven. However, ventriculolumbar perfusion of nimustine (ACNU) has been shown to be a safe and feasible treatment against subarachnoid dissemination of primary CNS tumors.[41] It is possible that this regimen may be an alternative for patients with diffuse metastases.

Radiation therapy is the most common treatment modality for metastatic spinal lesions (25–40 Gy in 2.5-Gy fractions).[77] While this therapeutic strategy may offer small improvements in neurological deficits and temporary pain relief, it has not demonstrated a significant survival advantage.[39] As the spinal metastasis of GBM becomes a more commonly reported complication, the development of new radiosurgical and chemotherapeutic techniques may become increasingly essential.

Future Treatment

Accumulating reports of extracranial metastases suggest that improved surveillance of the spine may be necessary in patients with GBM. Individuals with high-grade glial tumors who report back pain or radiculopathy should be evaluated with plain radiographs and MRI studies of the spine. Grabb et al.[31] suggest routine MRI of the craniospinal axis postoperatively, whereas Vertosick and Selker[77] promote surveillance of patients who survive more than 1 year after diagnosis of the primary intracranial disease. While early detection and treatment may not significantly affect survival given current therapeutic options, it would probably improve patient quality of life. Moreover, future prophylactic measures against metastatic disease may be capable of preventing spinal metastases, including intrathecally administered immunoconjugates capable of clearing malignant cells from the CSF. These immunoconjugates may prove beneficial for both prophylaxis and treatment of leptomeningeal gliomatosis.

Illustrative Case

History and Examination. A 60-year-old white man with a history of 2 left frontotemporal craniotomies as well as adjuvant chemotherapy and radiotherapy for GBM presented with primary symptoms of severe left lower-extremity pain and painful dysesthesias in the left lower buttock and posterior left thigh. Magnetic resonance imaging of the lumbar spine demonstrated a prominent focus of enhancement at the S-1 nerve root, eccentric to the left side. Despite initial medical management with neuroleptic agents, symptom progression led to imaging a month later, which showed an interval increase in the size of the previously indistinct intradural spinal nodule at the S-1 nerve root (Fig. 3). Given the growth of this nodule

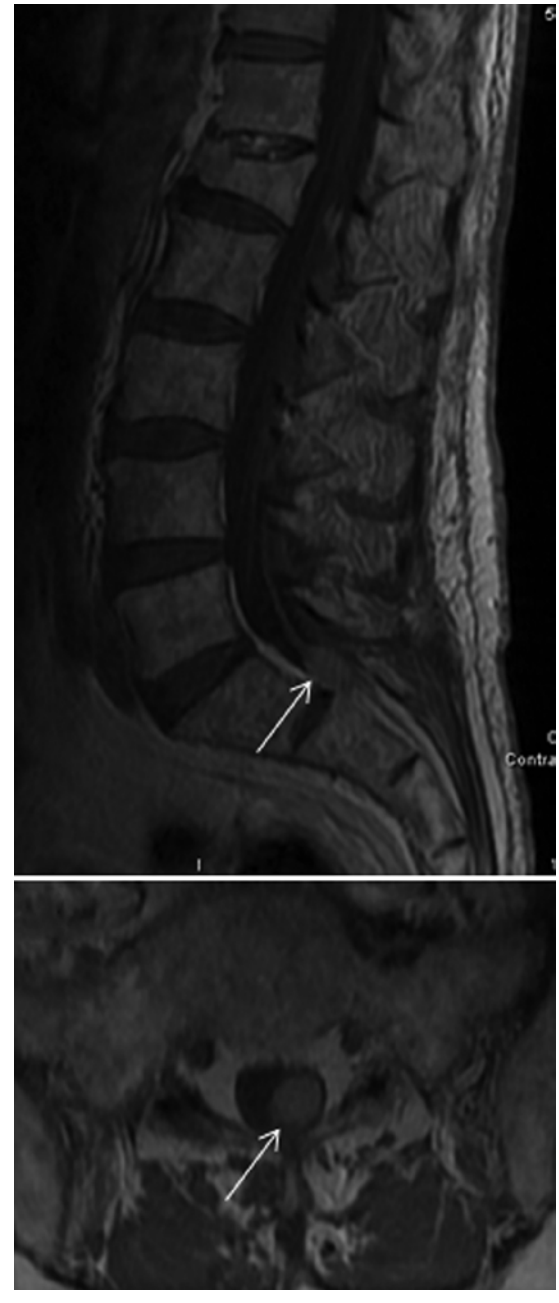

Fig. 3. Sagittal **(upper)** and axial **(lower)** Gd-enhanced T1-weighted MR images demonstrating a significant enhancing S1–2 level enhancing mass *(arrows)* with slight eccentricity to the left. A second area of enhancement can also be seen at L1–2 (upper).

as well as the patient's progressive left lower-extremity radiculopathy, we were concerned that this was a distant metastatic lesion.

Treatment. An initial lumbar puncture was performed for cytopathological studies and analysis of glioma markers in the CSF. Despite a sufficient tap volume, the findings were inconclusive. We elected to perform surgery primarily to obtain a diagnosis. We chose a minimally invasive, unilateral hemilaminotomy and partial medial facetectomy using serial muscle dilators and an expandable retractor (Quadrant, Medtronic, Inc.). This procedure allowed visualization under an operative microscope and direct biopsy of the significantly enlarged and pathological nerve root (Fig. 4). Using the operative microscope, we opened the nerve root sheath and dura of the S-1 nerve root. The nerve root itself was significantly larger than usual, and a soft grayish tumor was enveloping the contents of the nerve. The lesion was initially biopsied using pituitary forceps. Most of the tumor was serially debulked with a combination of Rhoton dissectors, and the dura was closed as previously described.[75] The total operative time was less than 90 minutes, and blood loss was less than 50 ml.

Posttreatment Course. Pathological diagnosis confirmed GBM, and the patient's radicular symptoms improved for 3 months prior to a significant progression in intracranial disease.

Conclusions

Although the outcome of patients with intracranial GBM remains invariably poor, improvements in outcomes have been increasingly observed within the last decade. However, the trend of better survival rates has paralleled a rising incidence of metastases to the spine. It is likely that with continued advancements in the management of primary intracranial lesions, spinal metastases will be an increasingly evident complication in patients with GBM. Knowledge of this likelihood, as well as the preventative measures and effective treatments for spinal lesions, will soon become a necessity. While no adequate therapy for metastatic disease has been proposed, we must continue to explore a number of management and preventative options.

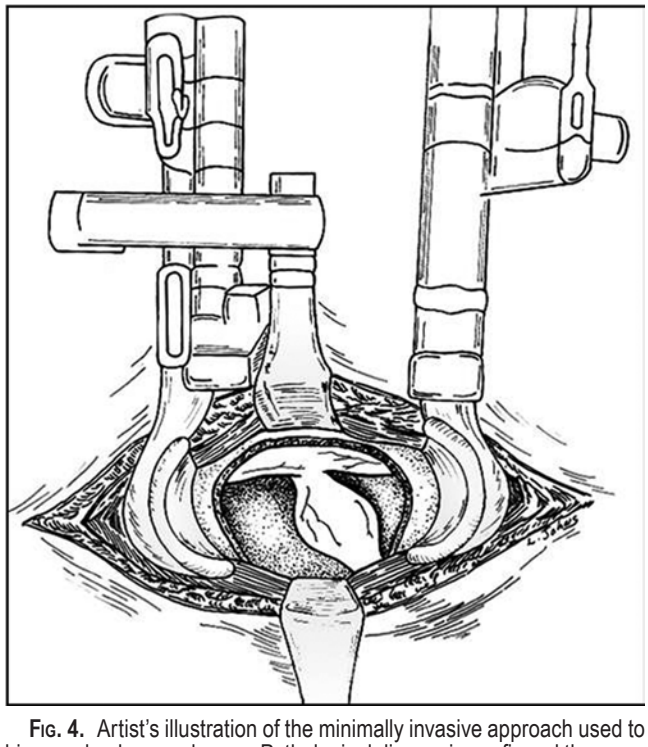

Fig. 4. Artist's illustration of the minimally invasive approach used to biopsy a lumbosacral mass. Pathological diagnosis confirmed the presence of an S-1 nerve root–associated high-grade glioma. A minimally invasive approach may decrease pain and morbidity in patients with a high disease burden. Printed with the permission of Lydia M. Johns, 2012.

Disclosure

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Author contributions to the study and manuscript preparation include the following. Conception and design: Smith. Acquisition of data: Lawton. Analysis and interpretation of data: Lawton, Nagasawa. Drafting the article: Lawton, Nagasawa. 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: Smith. Study supervision: Smith, Nagasawa, Yang, Fessler.

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References

1. Alatakis S, Malham GM, Thien C: Spinal leptomeningeal metastasis from cerebral glioblastoma multiforme presenting with radicular pain: case report and literature review. **Surg Neurol 56:**33–38, 2001
2. Ammerman JM, Kerr PB, Roberti F: Acute tetraplegia and cardiac arrest following high cervical leptomeningeal metastasis of giant cell glioblastoma. **J Clin Neurosci 18:**1133–1135, 2011
3. Anzil AP: Glioblastoma multiforme with extracranial metastases in the absence of previous craniotomy. Case report. **J Neurosurg 33:**88–94, 1970
4. Arita N, Taneda M, Hayakawa T: Leptomeningeal dissemination of malignant gliomas. Incidence, diagnosis and outcome. **Acta Neurochir (Wien) 126:**84–92, 1994
5. Arzbaecher J: Spinal metastasis in glioblastoma multiforme: a case study. **J Neurosci Nurs 39:**21–25, 2007
6. Barloon TJ, Yuh WT, Yang CJ, Schultz DH: Spinal subarachnoid tumor seeding from intracranial metastasis: MR findings. **J Comput Assist Tomogr 11:**242–244, 1987
7. Birbilis TA, Matis GK, Eleftheriadis SG, Theodoropoulou EN, Sivridis E: Spinal metastasis of glioblastoma multiforme: an uncommon suspect? **Spine (Phila Pa 1976) 35:**E264–E269, 2010
8. Brandes AA, Tosoni A, Franceschi E, Sotti G, Frezza G, Amistà P, et al: Recurrence pattern after temozolomide concomitant with and adjuvant to radiotherapy in newly diagnosed

patients with glioblastoma: correlation with MGMT promoter methylation status. **J Clin Oncol 27:**1275–1279, 2009
9. Bryan P: CSF seeding of intra-cranial tumours: a study of 96 cases. **Clin Radiol 25:**355–360, 1974
10. Buhl R, Barth H, Hugo HH, Hutzelmann A, Mehdorn HM: Spinal drop metastases in recurrent glioblastoma multiforme. **Acta Neurochir (Wien) 140:**1001–1005, 1998
11. Bukeo T, Matsumoto Y, Nishimoto A, Tabuchi K: [Spinal epidural metastasis of glioblastoma multiforme: a case report.] **No Shinkei Geka 13:**87–90, 1985 (Jpn)
12. Burger PC, Kleihues P: Cytologic composition of the untreated glioblastoma with implications for evaluation of needle biopsies. **Cancer 63:**2014–2023, 1989
13. Chang CC, Kuwana N, Ito S, Koike Y, Kitamura H: Spinal leptomeningeal metastases of giant cell glioblastoma associated with subarachnoid haemorrhage: case report. **J Clin Neurosci 8:**56–59, 2001
14. Chang YW, Yoon HK, Shin HJ, Roh HG, Cho JM: MR imaging of glioblastoma in children: usefulness of diffusion/perfusion-weighted MRI and MR spectroscopy. **Pediatr Radiol 33:**836–842, 2003
15. Choi WC, Lee JH, Lee SH: Spinal cord glioblastoma multiforme of conus medullaris masquerading as high lumbar disk herniation. **Surg Neurol 71:**234–237, 2009
16. Choucair AK, Levin VA, Gutin PH, Davis RL, Silver P, Edwards MS, et al: Development of multiple lesions during radiation therapy and chemotherapy in patients with gliomas. **J Neurosurg 65:**654–658, 1986
17. Ciappetta P, Salvati M, Capoccia G, Artico M, Raco A, Fortuna A: Spinal glioblastomas: report of seven cases and review of the literature. **Neurosurgery 28:**302–306, 1991
18. Cohen AR, Wisoff JH, Allen JC, Epstein F: Malignant astrocytomas of the spinal cord. **J Neurosurg 70:**50–54, 1989
19. Conti P, Pansini G, Mouchaty H, Capuano C, Conti R: Spinal neurinomas: retrospective analysis and long-term outcome of 179 consecutively operated cases and review of the literature. **Surg Neurol 61:**34–44, 2004
20. Corbett JJ, Newman NM: Symptomatic leptomeningeal metastases preceding other manifestations of occult primary brain tumors. **Surg Neurol 15:**362–367, 1981
21. Curran WJ Jr, Scott CB, Horton J, Nelson JS, Weinstein AS, Fischbach AJ, et al: Recursive partitioning analysis of prognostic factors in three Radiation Therapy Oncology Group malignant glioma trials. **J Natl Cancer Inst 85:**704–710, 1993
22. Davis FG, Freels S, Grutsch J, Barlas S, Brem S: Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histological type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973-1991. **J Neurosurg 88:**1–10, 1998
23. Elliott JP, Keles GE, Waite M, Temkin N, Berger MS: Ventricular entry during resection of malignant gliomas: effect on intracranial cerebrospinal fluid tumor dissemination. **J Neurosurg 80:**834–839, 1994
24. Erlich SS, Davis RL: Spinal subarachnoid metastasis from primary intracranial glioblastoma multiforme. **Cancer 42:**2854–2864, 1978
25. Erpolat OP, Akmansu M, Goksel F, Bora H, Yaman E, Büyükberber S: Outcome of newly diagnosed glioblastoma patients treated by radiotherapy plus concomitant and adjuvant temozolomide: a long-term analysis. **Tumori 95:**191–197, 2009
26. Fakhrai N, Czech T, Diekmann K, Fazeny-Dörner B, Birner P, Hainfellner JA, et al: Glioblastoma with spinal seeding. **Strahlenther Onkol 180:**455–457, 2004
27. Figueroa P, Lupton JR, Remington T, Olding M, Jones RV, Sekhar LN, et al: Cutaneous metastasis from an intracranial glioblastoma multiforme. **J Am Acad Dermatol 46:**297–300, 2002
28. Fine HA, Dear KB, Loeffler JS, Black PM, Canellos GP: Meta-analysis of radiation therapy with and without adjuvant chemotherapy for malignant gliomas in adults. **Cancer 71:** 2585–2597, 1993
29. Firsching R, Schröder R, Köning W, Frowein RA: [Spinal drainage metastasis in cerebral glioblastoma/gliosarcoma.] **Nervenarzt 56:**629–634, 1985 (Ger)
30. Giese A, Westphal M: Glioma invasion in the central nervous system. **Neurosurgery 39:**235–252, 1996
31. Grabb PA, Albright AL, Pang D: Dissemination of supratentorial malignant gliomas via the cerebrospinal fluid in children. **Neurosurgery 30:**64–71, 1992
32. Hamilton MG, Tranmer BI, Hagen NA: Supratentorial glioblastoma with spinal cord intramedullary metastasis. **Can J Neurol Sci 20:**65–68, 1993
33. Hata N, Katsuta T, Inoue T, Arikawa K, Yano T, Takeshita M, et al: [Extracranial metastasis of glioblastoma to the lung and heart with a histological resemblance to small cell carcinoma of the lung: an autopsy case.] **No Shinkei Geka 29:**433–438, 2001 (Jpn)
34. Hochberg FH, Pruitt A: Assumptions in the radiotherapy of glioblastoma. **Neurology 30:**907–911, 1980
35. Hübner F, Braun V, Richter HP: Case reports of symptomatic metastases in four patients with primary intracranial gliomas. **Acta Neurochir (Wien) 143:**25–29, 2001
36. Jahraus CD, Dishop MK, Bayliff SL, Lee C, St Clair WH: Atypical presentation and progression of glioblastoma multiforme in a 6-year-old girl: multidisciplinary case report. **J Pediatr Hematol Oncol 25:**243–247, 2003
37. Kalokhe G, Grimm SA, Chandler JP, Helenowski I, Rademaker A, Raizer JJ: Metastatic glioblastoma: case presentations and a review of the literature. **J Neurooncol 107:**21–27, 2012
38. Kanai R, Tasaka M, Sejima H, Uchida N, Nakano A, Akiyama Y, et al: Brain stem glioblastoma with multiple large cyst formation and leptomeningeal dissemination in a 4-year-old girl. **Brain Dev 27:**58–61, 2005
39. Karaca M, Andrieu MN, Hicsonmez A, Guney Y, Kurtman C: Cases of glioblastoma multiforme metastasizing to spinal cord. **Neurol India 54:**428–430, 2006
40. Kawanishi M, Kuroiwa T, Nagasawa S, Ohta T, Oketa M, Onomura T: [A case of spinal glioblastoma with intracranial dissemination.] **No Shinkei Geka 21:**1109–1112, 1993 (Jpn)
41. Kochi M, Kuratsu J, Mihara Y, Takaki S, Seto H, Uemura S, et al: Ventriculolumbar perfusion of 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosou rea hydrochloride. **Neurosurgery 33:**817–823, 1993
42. Kramer ED, Rafto S, Packer RJ, Zimmerman RA: Comparison of myelography with CT follow-up versus gadolinium MRI for subarachnoid metastatic disease in children. **Neurology 41:**46–50, 1991
43. Krex D, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M, et al: Long-term survival with glioblastoma multiforme. **Brain 130:**2596–2606, 2007
44. Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Nesbakken R, et al: Combined modality therapy of operated astrocytomas grade III and IV. Confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian Glioblastoma Study Group. **Cancer 47:**649–652, 1981
45. la Fougère C, Suchorska B, Bartenstein P, Kreth FW, Tonn JC: Molecular imaging of gliomas with PET: opportunities and limitations. **Neuro Oncol 13:**806–819, 2011
46. Lam CH, Cosgrove GR, Drislane FW, Sotrel A: Spinal leptomeningeal metastasis from cerebral glioblastoma. Appearance on magnetic resonance imaging. **Surg Neurol 35:**377–380, 1991
47. Lee SW, Fraass BA, Marsh LH, Herbort K, Gebarski SS, Martel MK, et al: Patterns of failure following high-dose 3-D conformal radiotherapy for high-grade astrocytomas: a quantitative dosimetric study. **Int J Radiat Oncol Biol Phys 43:**79–88, 1999
48. Lindsay A, Holthouse D, Robbins P, Knuckey N: Spinal leptomeningeal metastases following glioblastoma multiforme treated with radiotherapy. **J Clin Neurosci 9:**725–728, 2002

49. McGirt MJ, Goldstein IM, Chaichana KL, Tobias ME, Kothbauer KF, Jallo GI: Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients. **Neurosurgery 63:**55–61, 2008
50. Medhkour A, Chan M: Extremely rare glioblastoma multiforme of the conus medullaris with holocord and brain stem metastases, leading to cranial nerve deficit and respiratory failure: a case report and review of the literature. **Surg Neurol 63:**576–583, 2005
51. Megele R, Gruss P, Bührmann K: [Is extracranial metastatic malignant glioma iatrogenic?] **Neurochirurgia (Stuttg) 32:**157–159, 1989 (Ger)
52. Milano MT, Okunieff P, Donatello RS, Mohile NA, Sul J, Walter KA, et al: Patterns and timing of recurrence after temozolomide-based chemoradiation for glioblastoma. **Int J Radiat Oncol Biol Phys 78:**1147–1155, 2010
53. Minehan KJ, Shaw EG, Scheithauer BW, Davis DL, Onofrio BM: Spinal cord astrocytoma: pathological and treatment considerations. **J Neurosurg 83:**590–595, 1995
54. Naydenov E, Tzekov C, Minkin K, Nachev S, Romansky K, Bussarsky V: Long-term survival with primary glioblastoma multiforme: a clinical study in bulgarian patients. **Case Rep Oncol 4:**1–11, 2011
55. Oemus K, Gerlach H, Rath FW: [A rare complication of shunt therapy. Metastasis of brain tumors by cerebrospinal fluid drainage.] **Zentralbl Neurochir 53:**25–32, 1992 (Ger)
56. Oh J, Sahgal A, Sanghera P, Tsao MN, Davey P, Lam K, et al: Glioblastoma: patterns of recurrence and efficacy of salvage treatments. **Can J Neurol Sci 38:**621–625, 2011
57. Onda K, Tanaka R, Takahashi H, Takeda N, Ikuta F: Cerebral glioblastoma with cerebrospinal fluid dissemination: a clinicopathological study of 14 cases examined by complete autopsy. **Neurosurgery 25:**533–540, 1989
58. Onda K, Tanaka R, Takeda N: Spinal metastases of cerebral glioblastoma: the value of computed tomographic metrizamide myelography in the diagnosis. **Surg Neurol 25:**399–405, 1986
59. Park SH, Chi JG, Cho BK, Wang KC: Spinal cord ganglioglioma in childhood. **Pathol Res Pract 189:**189–196, 1993
60. Pohar S, Taylor W, Chandan VS, Shah H, Sagerman RH: Primary presentation of glioblastoma multiforme with leptomeningeal metastasis in the absence of previous craniotomy: a case report. **Am J Clin Oncol 27:**640–641, 2004
61. Preusser M, de Ribaupierre S, Wöhrer A, Erridge SC, Hegi M, Weller M, et al: Current concepts and management of glioblastoma. **Ann Neurol 70:**9–21, 2011
62. Salazar OM, Rubin P: The spread of glioblastoma multiforme as a determining factor in the radiation treated volume. **Int J Radiat Oncol Biol Phys 1:**627–637, 1976
63. Sanai N, Berger MS: Operative techniques for gliomas and the value of extent of resection. **Neurotherapeutics 6:**478–486, 2009
64. Sanborn MR, Pramick M, Brooks J, Welch WC: Glioblastoma multiforme in the adult conus medullaris. **J Clin Neurosci 18:**842–843, 2011
65. Schuster H, Jellinger K, Gund A, Regele H: Extracranial metastases of anaplastic cerebral gliomas. **Acta Neurochir (Wien) 35:**247–259, 1976
66. Scoccianti S, Detti B, Meattini I, Iannalfi A, Sardaro A, Leonulli BG, et al: Symptomatic leptomeningeal and intramedullary metastases from intracranial glioblastoma multiforme: a case report. **Tumori 94:**877–881, 2008
67. Seppälä MT, Haltia MJ, Sankila RJ, Jääskeläinen JE, Heiskanen O: Long-term outcome after removal of spinal schwannoma: a clinicopathological study of 187 cases. **J Neurosurg 83:**621–626, 1995
68. Shah A, Redhu R, Nadkarni T, Goel A: Supratentorial glioblastoma multiforme with spinal metastases. **J Craniovertebr Junction Spine 1:**126–129, 2010
69. Smith DR, Hardman JM, Earle KM: Metastasizing neuroectodermal tumors of the central nervous system. **J Neurosurg 31:**50–58, 1969
70. Stark AM, Nabavi A, Mehdorn HM, Blömer U: Glioblastoma multiforme-report of 267 cases treated at a single institution. **Surg Neurol 63:**162–169, 2005
71. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. **Lancet Oncol 7:**392–401, 2006
72. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, et al: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. **Lancet Oncol 10:**459–466, 2009
73. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. **N Engl J Med 352:**987–996, 2005
74. Toledano Delgado R, Garcia N, Riva-Amarante E, Rodríguez Pascual J, García Leal R, Sendra Tello J: [Spinal leptomeningeal metastasis from cerebral glioblastoma: case report.] **Neurologia 21:**378–381, 2006 (Span)
75. Tredway TL, Santiago P, Hrubes MR, Song JK, Christie SD, Fessler RG: Minimally invasive resection of intradural-extramedullary spinal neoplasms. **Neurosurgery 58 (1 Suppl):**ONS52–ONS582006
76. Tseng HM, Kuo LT, Lien HC, Liu KL, Liu MT, Huang CY: Prolonged survival of a patient with cervical intramedullary glioblastoma multiforme treated with total resection, radiation therapy, and temozolomide. **Anticancer Drugs 21:**963–967, 2010
77. Vertosick FT Jr, Selker RG: Brain stem and spinal metastases of supratentorial glioblastoma multiforme: a clinical series. **Neurosurgery 27:**516–522, 1990
78. Yung WA, Horten BC, Shapiro WR: Meningeal gliomatosis: a review of 12 cases. **Ann Neurol 8:**605–608, 1980

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Address correspondence to: Zachary A. Smith, M.D., Department of Neurological Surgery, Suite 2210, Northwestern University, 676 North St. Clair Street, Chicago, Illinois 60661. email: zsmithmd@gmail.com.