JOURNAL OF NEUROSURGERY:
Case Lessons

J Neurosurg Case Lessons 6(25): CASE23296, 2023
DOI: 10.3171/CASE23296

Long-term survival after cordectomy in a case of spinal cord diffuse midline glioma, H3K27-altered: illustrative case

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BACKGROUND Spinal cord diffuse midline glioma, H3K27-altered, is an extremely rare entity with a poor prognosis. However, its optimal treatment remains poorly defined. Although cordectomy was introduced in the early 20th century, its efficacy has been questioned and shrouded behind the scenes.

OBSERVATIONS A 76-year-old male with recent-onset paraparesis of the lower extremities and paresthesia presented to our outpatient clinic. Magnetic resonance imaging revealed an intra-axial spinal cord tumor extending from T12 to L2. The patient underwent laminectomy and partial tumor resection, and the surgical specimen was histologically diagnosed as a diffuse midline glioma, H3K27-altered. Although standard chemoradiotherapy was implemented, the patient experienced local tumor recurrence 2 years later and underwent cordectomy at T9. The patient was alive at the 4-year follow-up after cordectomy without tumor recurrence. According to the literature, patients with lesions in the lower thoracic cord below T8 achieved a longer survival than those with lesions in the upper thoracic cord above T5.

LESSONS Cordectomy benefits selected cases of high-grade spinal cord gliomas. Maximal prevention of cerebrospinal fluid dissemination by tumor cells is indisputably important, and tumors located below the lower thoracic spine may be the key to success in establishing a long-term prognosis after cordectomy.

https://thejns.org/doi/abs/10.3171/CASE23296

KEYWORDS cordectomy; spinal cord diffuse midline glioma; H3K27M-altered; long survival

Spinal cord World Health Organization (WHO) grade 4 glioma is an extremely rare entity, accounting for 1.5% of all spinal cord tumors.[1] Spinal cord WHO grade 4 glioma includes histopathologically proven glioblastoma and genomically classified diffuse midline glioma, H3K27-altered.[2] To date, fewer than 200 cases of spinal cord glioblastoma have been reported,[3] and because spinal cord diffuse midline glioma is a relatively novel entity, the number of reported cases is further limited.[2] Moreover, the prognosis remains dismal; median overall survival (mOS) of patients with spinal cord glioblastoma has been reported to be approximately 12 months.[3] This falls below the mOS of its supratentorial counterpart, which ranges from 15 to 22 months.[4,5] Although ill-defined, the mOS of spinal cord diffuse midline glioma is also dismal, which has been reported to be 17.0 ± 3.7 months.[2] Optimal treatment remains indistinct, and most cases are treated with subtotal tumor resection or biopsy followed by radiotherapy with or without chemotherapy.[6,7] The impact of the extent of resection is controversial, and the preservation of neurological function is emphasized.[3,7,8]

Cordectomy is a radical treatment that amputates the spinal cord rostrally to the lesion, together with closure of the thecal sac, and is generally recognized as an irreversible and final option.[9] Since its inception in 1916, cordectomy has been applied to a variety of spinal pathologies.[9] Spinal cord glioblastoma cordectomy was first conducted in 1949, resulting in a postoperative survival of 6.5 months.[10] Despite its early introduction, according to the literature, only nine cases of cordectomy for spinal cord glioblastoma have been reported to date, and there have been no reports of cordectomy for spinal cord diffuse midline glioma, H3K27-altered.[6,10–15] There is a paucity of evidence regarding its application and skepticism regarding its efficacy in disease control.

ABBREVIATIONS CSF = cerebrospinal fluid; MRI = magnetic resonance imaging; mOS = median overall survival; WHO = World Health Organization.
INCLUDE WHEN CITING Published December 18, 2023; DOI: 10.3171/CASE23296.
SUBMITTED June 6, 2023. **ACCEPTED** November 1, 2023.

Spinal cord grade 4 glioma is proposed to spread via two mechanisms: dissemination through the leptomeningeal pathway[8] and contiguous extension/invasion along the nerve fiber bundles.[16] Theoretically, cordectomy forestalls both mechanisms by blocking the cerebrospinal fluid (CSF) route and severing the nerve fiber pathway to infiltrate. The patient in the current study with spinal cord diffuse midline glioma had a long survival without tumor recurrence after cordectomy. Here, we illustrate our experience and appraise the literature to elucidate the optimal application of cordectomy.

Illustrative Case

A 76-year-old male presented to our outpatient clinic complaining of progressive paraparesis of the lower extremities and numbness for the past 2 months. Additionally, he had experienced recent-onset bladder and bowel dysfunctions. His medical history included hepatitis C virus infection and an L3 to L5 intervertebral fusion for lumbar spinal canal stenosis. Magnetic resonance imaging (MRI) revealed an enlarged lumbar spinal cord extending from T12 to L2 and corresponding canal stenosis from T12 to L3 (Fig. 1A). An intramedullary tumor in the spinal cord was suspected. The patient underwent lumbar laminectomy from L1 to L3 and partial resection of the spinal cord tumor (Fig. 1B). Histologically, the tumor showed massive infiltration of highly pleomorphic cells with abundant microvasculature (Fig. 1C). Immunohistochemical staining for H3K27M mutant protein revealed strong nuclear positivity in the tumor cells (Fig. 1D). The mean MIB-1 index was 25.5%. Accordingly, a diagnosis of diffuse midline glioma, H3K27-altered, was made.

The patient underwent fractionated radiotherapy (54 Gy/27 fractions) and concomitant temozolomide treatment, followed by 12 cycles of adjuvant temozolomide. He had been free from tumor progression on regular imaging follow-up every 2 months until MRI revealed an intramedullary, heterogeneously enhanced lesion extending from T10 to L2 at 2 years after the initial surgery (Fig. 2A and B). Therefore, tumor recurrence was suspected. Because there was no other effective therapeutic option and the function of his lower extremities was already irreversibly disabled, the decision to perform a cordectomy was made. The patient underwent a lower thoracic laminectomy and cordectomy at T9 (Fig. 2C and D). The thecal sac was closed at T9 with 4-0 Prolene sutures (Ethicon, Johnson and Johnson) in a water-tight fashion. The histopathological diagnosis was congruent with the recurrence of a diffuse midline glioma, H3K27-altered. Postoperatively, syrinx formation was observed in the spinal cord. It temporarily progressed to the upper thoracic level but subsequently resolved on its own. The patient remained asymptomatic throughout the postoperative course and underwent six additional cycles of temozolomide. The patient was monitored at the outpatient clinic with regular imaging follow-ups, without any evidence of tumor recurrence in the neuraxis for 6 years after the initial surgery and 4 years after cordectomy (Fig. 3).

Patient Informed Consent

The necessary patient informed consent was obtained in this study.

Discussion

Observations

Cordectomy is a neurosurgical procedure that irreversibly transects the spinal cord above the lesion with an ample margin and permanent closure of the thecal sac. This procedure is a potentially viable option, especially in cases of profound deficits below the planned level of transection.[12] Severing the nerve fibers and segregating the CSF space obviate the potential routes for tumor extension along the spinal cord and via the CSF by isolating the rostral central nervous system, which theoretically thwarts tumor dissemination. Despite these conceivable benefits, cordectomy is far from the mainstay of treatment for

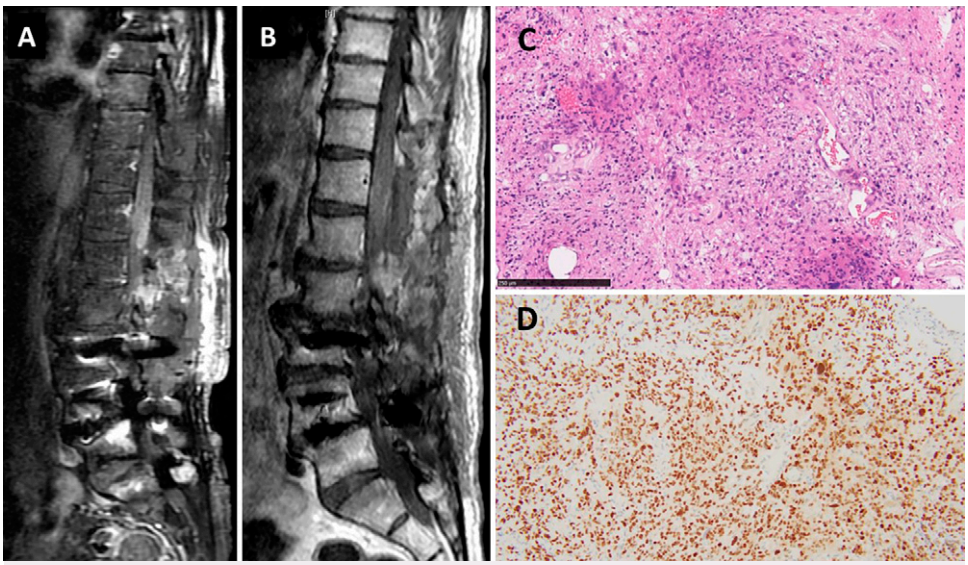

FIG. 1. Enhanced T1-weighted image revealed an enlarged lumbar spinal cord extending from T12 to L2 (**A**). Strong metal artifacts were evident due to L3 to L5 intervertebral fusion for lumbar spinal canal stenosis. Partial resection of the spinal cord tumor was performed (**B**). Histologically, the tumor had massive infiltration of highly pleomorphic cells with abundant microvasculature (**C**, hematoxylin and eosin, original magnification ×250). Immunohistochemical staining for histone H3K27M mutant protein revealed a strong nuclear positivity in tumor cells (**D**, original magnification ×280).

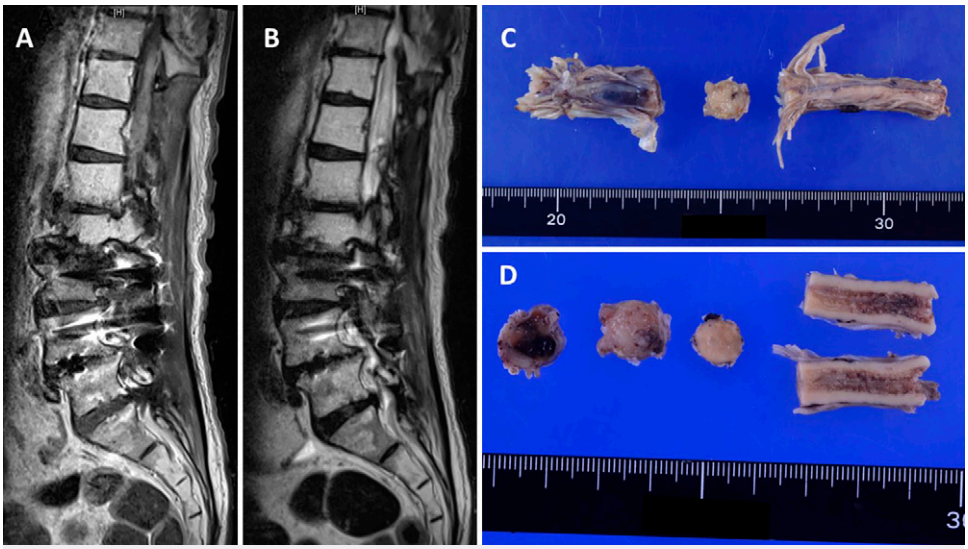

FIG. 2. Enhanced T1-weighted image revealed an intramedullary, heterogeneously enhanced lesion extending from T10 to L2 a year after the initial surgery (**A**). A T2-weighted image showed an enlarged edematous spinal cord (**B**). The patient underwent lower thoracic laminectomy and cordectomy below T9. The transected spinal cord was submitted for pathological evaluation (**C**). The affected spinal cord was enlarged and partially necrotic with hemorrhagic components. Cross-sectioning revealed infiltration of the tumor and the resultant destruction of the boundaries between white matter and gray matter of the spinal cord (**D**).

spinal cord tumors. Reasons for its unpopularity would include the potential for untoward sequelae with complete loss of neurological functions below the transected spinal level, and no definitive criteria for the selection of cases have been examined.[9] Only nine cases of spinal cord grade 4 glioma treated with cordectomy have been reported in the literature, and all were diagnosed as glioblastoma.[6,10,12,14,15] There are no reports regarding cordectomy applied to diffuse midline glioma, H3K27-altered. This paucity of evidence supposedly reflects the skepticism of radical treatment. However, based on our current case, which achieved a long survival after cordectomy, as well as several previous cases with moderately long survival, viewing this surgical technique as favorable in selected cases may be reasonable. We propose that a tumor involving the lower thoracic region that displays complete functional loss below the affected level is an optimal candidate for cordectomy.

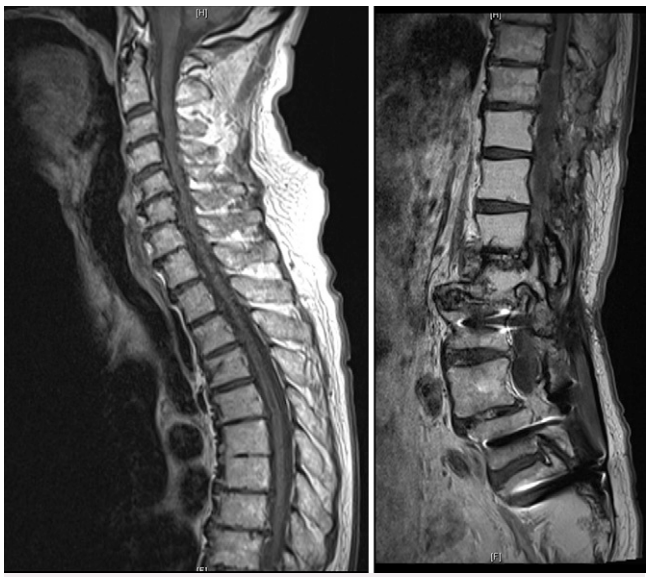

FIG. 3. Follow-up imaging 6 years after the initial surgery and 4 years after cordectomy revealed no recurrence (**left and right**). Notably, enhanced T1-weighted imaging demonstrated the transected spinal cord at T9.

All previously published cases and our experience are summarized in Table 1. Although three cases succumbed within a year after cordectomy, six cases survived for more than a year. One patient even survived for 135 months after cordectomy, which was the longest survival.[12] The median survival after cordectomy was 26 months. Six patients, including our patient, survived longer than 1 year (range, 16–135 months), and the median survival was 43.5 months. In a comparison of short-survival ($<$1 year) and long-survival ($>$1 year) groups, the short-survival group demonstrated a higher (rostral) tumor location in the upper thoracic spinal cord (T2–3). In contrast, the long-survival group exhibited a lower tumor location (T5–12), which assumingly enabled the performance of cordectomy with a sufficient margin of more than three spine levels. Innervation of the respiratory muscles by the cervical spine and upper extremities by the cervicothoracic spine above the T2–3 level limits cordectomy with a sufficient margin in cases with upper thoracic spinal cord involvement.[15] Of note, dissemination was the leading cause of death in both groups, and to our surprise, none of the reported cases experienced local recurrence or contiguous tumor invasion above the level of cordectomy. This result suggests that cordectomy obstructs tumor spread along the nerve fibers.

Considering these findings, although the number of reported cases remains limited, we presume that the following points are essential for discussing long-term control of spinal cord glioblastoma or diffuse midline glioma after cordectomy.

Tumor location was the most important factor. Upper thoracic level involvement makes cordectomy with a sufficient margin less

TABLE 1. Summary of the published cases and our case

Case No.	Authors & Year	Age (yrs)/Sex	Pathology	Initial Tumor Location	Physical Examination	FU After Cordectomy (mos)	Outcome	No. of Prior Ops	Adjuvant Therapy	Level of Cordectomy	Contiguous Invasion Above Level of Cordectomy	Dissemination
1	MacCarty & Keifer, 1949[10]	25/M	Glioblastoma	Thoracic	Paraplegia, bowel-bladder incontinence, sensory loss at T2	6.5	Dead	2	No	Thoracic, lumbar, sacral	NA	NA
2	Marchan et al., 2007[14]	50/M	Glioblastoma	T11	Paraplegia, bowel-bladder incontinence, complete sensory loss below	79	Dead	1	CMT + RT	Thoracic	No	Cerebellar metastasis
3	Nakamura et al., 2010[15]	13/M	Glioblastoma	T2	Frankel grade A	4	Dead	0	NA	T1–2	No	Dissemination
4		63/M	Glioblastoma	T3	Frankel grade A	5	Dead	0	NA	T1–2	No	Dissemination
5		42/M	Glioblastoma	T5	Frankel grade C	16	Alive	1	NA	T2–3	No	No
6		49/M	Glioblastoma	T8	Frankel grade C	39	Alive	1	NA	T2–3	No	No
7	Konig et al., 2010[6]	56/M	Glioblastoma	T12	NA	26	Dead	1	RT	T3	No	Septum pellucidum metastasis
8	Viljoen et al., 2014[12]	47/M	Glioblastoma	T8–9	ASIA C, T8 sensory level	135	Dead	1	CMT + RT	Thoracic	No	Lt frontal lobe & lt occipital lobe metastasis
9	Present case	76/M	Diffuse midline glioma, H3K27-altered	T10–L2	Paraplegia, bowel-bladder incontinence, complete sonsory loss below	48	Alive	1	CMT + RT	T9	No	No

ASIA = American Spinal Injury Association; CMT = chemotherapy; FU = follow-up; NA = not available; RT = radiotherapy.

feasible for the aforementioned reasons. Furthermore, the proximity of the lesion to the intracranial space might make intracranial extension or dissemination more likely. Tumors located in the upper thoracic region showed early dissemination, whereas those located in the lower region had relatively late dissemination (follow-up period until death: 4–5 vs 16–135 months).

Regarding the importance of distance to the intracranial space from the tumor in prognosis, Timmons et al.[3] performed a systematic review of spinal cord glioblastoma and found that long-term survivors were all afflicted by tumors that occurred in the thoracic cord versus the cervical cord. This tendency was also true for spinal cord diffuse midline glioma. Patients with thoracic cord tumors exhibited a better prognosis than those with cervical cord tumors (31.0 ± 6.0 vs 10.0 ± 4.8 months).[2] Patients with tumors in the thoracic spinal cord exhibit a 0.261 times higher risk of death than those with tumors in the cervical segment.[2] The authors concluded that these finding were explainable by the feasibility of aggressive treatment in the lower spinal cord, such as surgery and high-dose radiation.

Although chemoradiotherapy has not been proved to improve the prognosis in spinal cord glioblastoma,[3] it does serve as a pragmatic therapy without other feasible treatment options. For cordectomy to be a truly viable option for spinal cord WHO grade 4 glioma, in addition to chemoradiotherapy, considering treatment failure is closely linked with intracranial extension. Furthermore, ways to circumvent CSF dissemination remain an arduous challenge to overcome. A patient with preexisting dissemination would not be a good candidate because this aggressive treatment would be futile. Furthermore, this surgical treatment should be balanced with alternative therapeutic options including novel targeted therapies and immunotherapies, such as ONC201 or GD2-CAR T-cell therapy.[17–20] Ideally, highly effective medical treatments could obviate or significantly delay the need for aggressive surgery in the future. Cordectomy should be strictly indicated only for patients with pathological confirmation, complete functional loss below the affected level, resistance to other treatment options, and no evidence of extensive dissemination.

Lessons

Here, we presented a case of spinal cord diffuse midline glioma, H3K27-altered, with a long survival after cordectomy. Selected patients might benefit from cordectomy. A literature review indicates that a tumor located in the lower thoracic region, which presents with preexisting complete functional loss below the affected level and absence of dissemination, can be a suitable candidate.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Tanaka, Sato, Takami, Takayanagi. Acquisition of data: Tanaka, Sato. Analysis and interpretation of data: Tanaka, Sato, Takami, Ikemura. Drafting the article: Sato, Takami. Critically revising the article: Tanaka, Takami, Takayanagi. Reviewed submitted version of manuscript: Tanaka, Takami, Takayanagi, Ikemura, Saito. Approved the final version of the manuscript on behalf of all authors: Tanaka. Administrative/technical/material support: Tanaka, Ikemura. Study supervision: Tanaka, Takami.

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