# Prolonged survival of a patient with cervical intramedullary glioblastoma multiforme treated with total resection, radiation therapy, and temozolomide

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**We report a case of prolonged survival in a patient with cervical intramedullary glioblastoma multiforme (GBM) treated with total resection, radiotherapy, and temozolomide. A 26-year-old woman complaining of midline lower cervical pain, insidiously progressive motor weakness, paresthesia, and urinary incontinence was admitted to our institution. MRI showed an intramedullary mass lesion in the C2–C6 level, which was considered to be an ependymoma or astrocytoma. Total resection of the tumor was performed at the C2–C6 level by laminoplasty with miniplate, followed by chemoradiotherapy (focal irradiation dose of 5000, at 200 cGy per fraction for over a period of 5 weeks) with concomitant temozolomide (75 mg/m$^2$). Histologic examination of the resected tumor confirmed GBM. The tumor consisted of a markedly pleomorphic neoplasm measuring 4.6 cm × 2.6 cm × 1.7 cm and characterized by necrosis, atypical mitotic figures, and endothelial proliferation. Postoperative MRI showed a centrally located, postoperative cavity at the C2–C6 level. Recurrence in the cervical spine without brain GBM metastasis was identified 25 months after operation, and temozolomide chemotherapy was reinitiated; however, the tumor progressed, and the patient died 33 months after operation. We suggest that, in addition to potential factors of tumor biology, multimodal treatment consisting of total resection of intramedullary GBM coupled with radiation therapy and temozolomide may have prolonged the survival of this patient.** *Anti-Cancer Drugs* **21:963–967**


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## Introduction

Intramedullary spinal cord tumors are relatively rare primary central nervous system tumors, representing approximately 5% of all spinal neoplasms in adults [1]. The majority of these spinal cord tumors are low-grade astrocytomas or ependymomas, depending on the age of the patient and the level of the spinal cord involved [2,3]. Malignant high-grade gliomas are uncommon with anaplastic astrocytomas accounting for approximately 15% of all intraspinal tumors, and glioblastoma multiforme (GBM) accounting for only 1–5% of all glioblastomas [2]. Intraspinal anaplastic astrocytomas and GBMs possess similar histopathological features, and the prognostic implications are similar to those of corresponding tumors at other sites in the central nervous system [4]. When aggressive/radical excision is attempted, the survival time of patients with spinal GBM is shorter than that of patients with anaplastic astrocytoma [5]. Traditional surgical management of high-grade, intraspinal tumors predominantly involves limited excision or diagnostic biopsy followed by radiotherapy and adjuvant chemotherapy. Here we report a case of cervical intramedullary GBM treated by total resection followed by radiotherapy and chemotherapy with temozolomide, an oral alkylating agent indicated for the treatment of intracranial GBM. The patient survived for 33 months (25 months disease free) after the operation.

## Case summary

A 26-year-old woman complaining of posterior midline, lower cervical pain; insidiously progressive motor weakness, paresthesia, and grade 2 urinary incontinence (Common Terminology Criteria for Adverse Events, v. 3.0), which had developed over a period of several weeks and lasted for 4 months was admitted to our institution. Pain in the lower neck was exacerbated when turning to the side, lying down, coughing, or laughing. Two months after noticing progressive motor weakness of the right upper limb, she was admitted to a local hospital with sudden onset of anuria, dyspnea, and hemiplegia. She received intravenous steroid treatment and was

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discharged a month later after recovering sufficient strength of the extremities to walk, and with urinary incontinence recovered to grade 1.

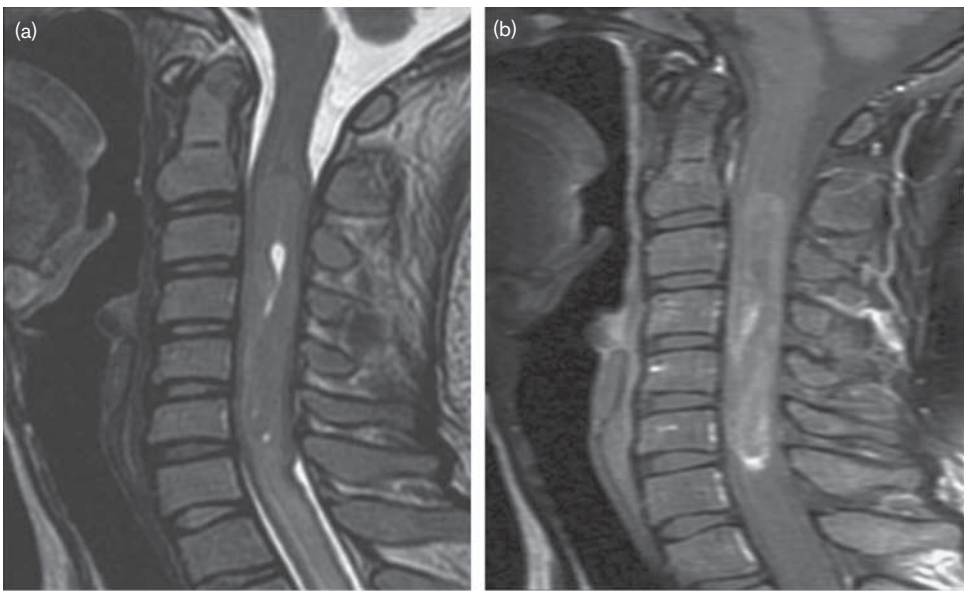
Neurological examination upon admission at our institution showed weakness of the bilateral upper and lower extremities, bilateral lower limb hyperreflexia, and decreased sensation to pinprick below the level of C4. Cervical magnetic resonance imaging (MRI) performed on the same day showed an intramedullary mass lesion at the C2–C6 level (Fig. 1), which was considered to be an ependymoma or an astrocytoma. Two days later, total resection of the tumor was performed at the C2–C6 level by laminoplasty with miniplate. Midline myelotomy showed a grayish, elastic, soft tumor at the C2–C6 level. The tumor margin from the spinal cord was ill-defined, but was distinct enough to merit complete excision.

The original impression according to MRI results was an intramedullary astrocytoma or ependymoma; however, intraspinal GBM was diagnosed according to pathology analysis. The tumor consisted of a markedly pleomorphic neoplasm measuring $4.6 \times 2.6 \times 1.7$ cm and was characterized histopathologically by necrosis, atypical mitotic figures, and endothelial proliferation. Immunohistochemically, the tumor was diffusely positive for glial fibrillary acidic protein staining (Fig. 2a), confirming a glial tumor. Microscopically, necrosis (Fig. 2b) and endothelial proliferation (Fig. 2c) were present and GBM was diagnosed.

The methylation status of the *O*-6-methylguanine DNA methyltransferase (MGMT) promoter was analyzed by methylation-specific polymerase chain reaction, and the results showed that the promoter was unmethylated (data not shown). Chromosomal alterations of 1p/19q were also analyzed by quantitative microsatellite analysis and real-time polymerase chain reaction, and the results showed no 1p/19q loss in this tumor (data not shown) [6].

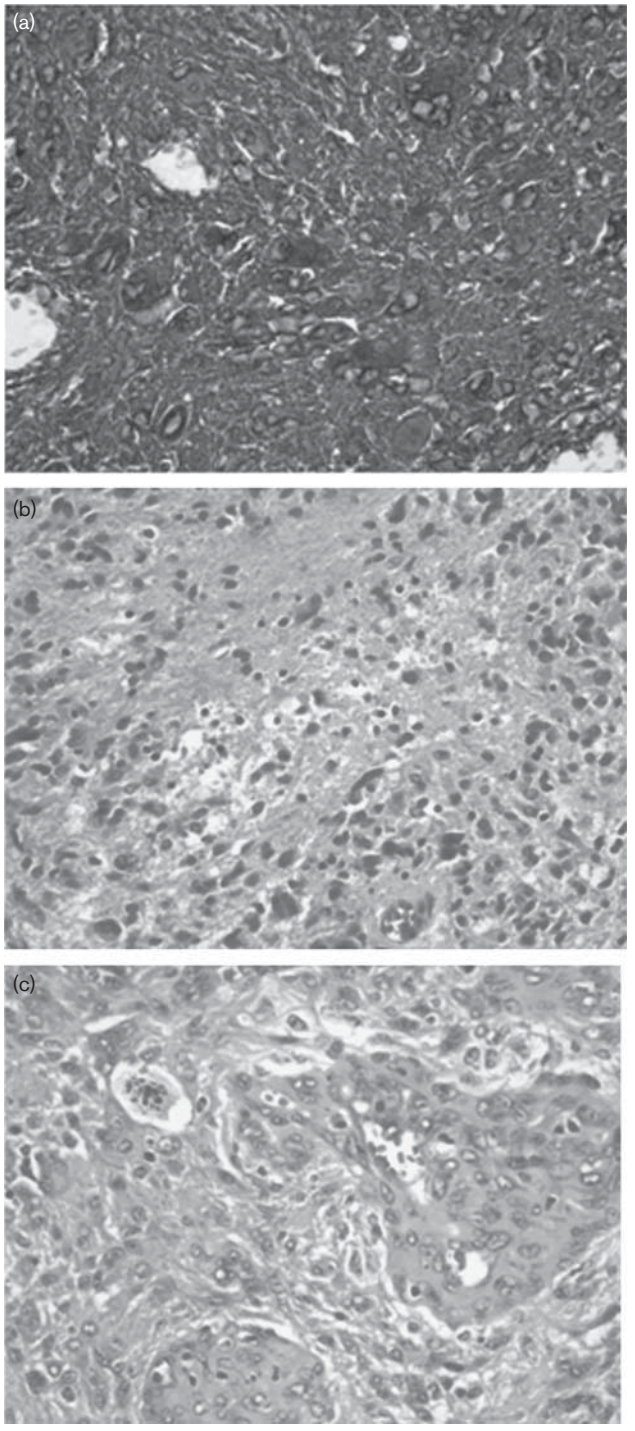
Cerebral MRI 5 days after the operation showed no obvious intracranial lesions. However, mild edematous changes were present in the lower medulla oblongata and upper spinal cord levels related to the tumor site. Cervical spinal MRI in the anteroposterior and lateral views showed normal alignment but internal fixation of posterior elements at the C2–C7 level. No other remarkable findings were noted. Six days after total resection, cervical MRI showed a centrally located, postoperative cavity at the C2–C6 level characterized by hypointensity on T1-weighted image, hyperintensity on T2-weighted image, and rim enhancement on contrast-enhanced T1-weighted image (Fig. 3). Edematous changes in the spinal cord were observed from the lower brainstem to the T5 level. Two weeks later, the patient began with chemoradiotherapeutic treatment as follows: three-dimensional conformal radiotherapy with 6 MV linear accelerator photon beams delivered to the tumor site for a total focal dose of 5000, at 200 cGy per fraction for 25 fractions, with a 0.5 cm margin, and concomitant temozolomide daily dose of 75 mg/m$^2$ for a period of 5 weeks.

**Fig. 1**




(a) Sagittal T2-weighted magnetic resonance image shows an expansile intramedullary mass from level C2–C6, with intermediate signal intensity and some small cystic parts. There was also edematous change of the spinal cord below level C6. (b) Postcontrast sagittal T1-weighted magnetic resonance image with fat saturation shows heterogeneous enhancement of this lesion.

**Fig. 2**

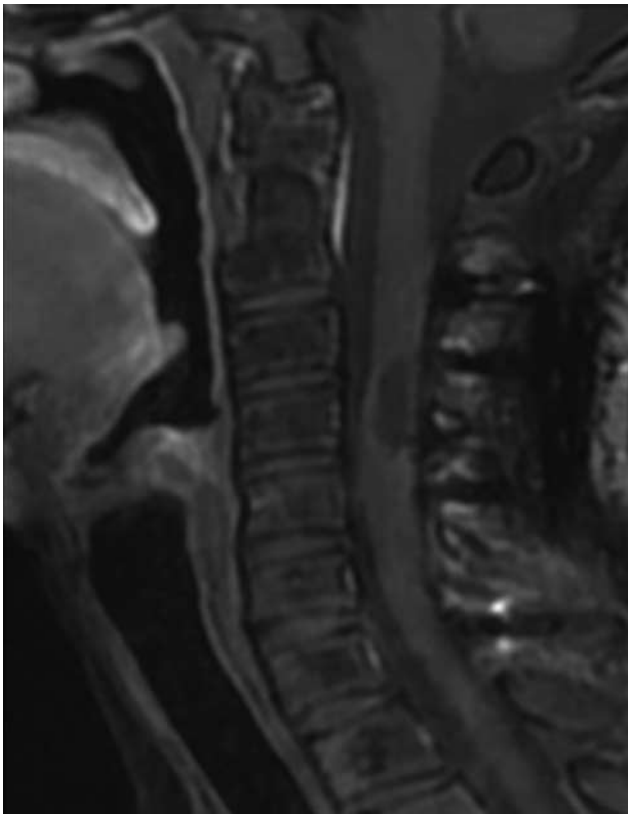



The tumor was composed of pleomorphic tumor cells within a fibrillary background. Positive staining for glial fibrillary acidic protein (a) was present in the fibrillary background. Necrosis (b) and endothelial proliferation (c) were present. Glioblastoma multiforme was diagnosed.

Three days after completion of radiation and chemotherapy treatments, the patient was transferred to our intensive rehabilitation program, and underwent endurance exercise and ambulation training with a quadricane and anterior-type ankle–foot orthoses under contact guard for approximately 10 m. On transfer, the patient exhibited increased weakness of the right upper and lower extremities, bilateral Babinski reflex, decreased sensation to touch and pinprick at C5 and T1–T12, and anesthesia at the C6–C8 level. Urinary incontinence resolved (grade 0), but increased urinary frequency was observed after the operation. The total Barthel Index score is a validated and reliable measurement tool for daily living activities [7,8]. The total Barthel Index score of the patient was 25 (feeding 5, transfer 0, grooming 5, toilet use 0, bathing 0, mobility 0, stairs 0, dressing 0, bowels 5, bladder 10). The patient was subsequently discharged in a stable condition with a custom-made wheelchair. Cervical MRI at the 1-month follow-up showed focal, abnormal, well-defined cerebrospinal fluid-like signal intensity in the spinal cord at the C3–C4 level, with minimal wall enhancement, which had resolved by the 4-month follow-up.

Postoperative follow-ups at 8, 12, 16, and 20 months showed normal findings. However, a follow-up MRI at 25 months showed a recurrence in the cervical spine,

**Fig. 3**



After treatment, a postcontrast sagittal T1-weighted magnetic resonance image with fat saturation showed a cavity in the spinal cord at the level of C3–C4, without abnormal enhancement; there was no evidence of tumor recurrence.

without progression of neurologic deficits. No signs of brain GBM metastasis were detected. However, pain in the left shoulder and back and weakness of the left arm was noted a month later, and an additional MRI showed tumor progression and rapid regrowth. Twenty-one days after the initial identification of recurrence, the patient began treatment with oral temozolomide 200 mg/m$^2$ for 5 days every 4 weeks, for a total of seven cycles. An MRI 3.5 months later showed a decrease in tumor size. Nonetheless, the patient entered into hospice care with a diagnosis of cervical GBM status post-tumor excision with concurrent chemoradiotherapy and incomplete tetraplegia, owing to progressive dyspnea upon sitting up along with gradual loss of posture sensory function. The patient died 33 months after operation.

## Discussion

The present patient experienced a better outcome than average after multimodal treatment consisting of total resection combined with radiation therapy and temozolomide, showing improvements in neurologic and motor functions until the 25-month follow-up, with a 33-month survival period. Spinal intramedullary GBM has been rarely reported. However, there is a recent report of a patient with a 26-month survival period [9]. Treatment consisted of surgical debulking of the tumor, radiation therapy, and nimustine hydrochloride. That patient subsequently died as a result of intracranial tumor dissemination. This patient did not develop brain GBM metastasis. Treatment with temozolomide in combination with radiation therapy has shown long-term benefits for patients with brain GBM [10]. Given the histological similarities between brain and spinal GBM [11], these forms may have biological similarities and similar responses to chemotherapeutic agents, including temozolomide.

The prognosis for intramedullary GBM is very poor (median, 15 months; range, 6–18 months) and leptomeningeal spread occurs in approximately 60% of these patients [1–5,12]. As a result, the correct diagnosis of GBM is critically important. According to the 2007 WHO classification, GBM (grade 4) has a histological appearance similar to anaplastic astrocytoma (grade 3; showing anaplasia and mitotic activity) with the additional features of necrosis and microvascular or endothelial cell proliferation (an apparent multilayering of endothelium) [13]. To ensure that the diagnosis of GBM is correct, two pathologists reviewed the pathological slides of this patient. Microscopically, the tumor was composed of pleomorphic tumor cells in a fibrillary background. Mitoses with atypical figures were frequently observed. The presence of necrosis (Fig. 2b) and microvascular proliferation (Fig. 2c) in addition to cellular atypism and pleomorphism justify the diagnosis of GBM as opposed to anaplastic astrocytoma.

Extensive resection is difficult in intramedullary GBM, owing to its ill-defined tumor margin from the spinal cord and adjacent tissues and overall poor prognosis irrespective of therapeutic intervention [14]. The high risk of serious postoperative neurological consequences has led many institutions to resort to diagnostic biopsy or partial resection followed by radiation and adjuvant chemotherapy. In this case, the cleavage plane of the tumor was sufficiently defined to justify complete surgical resection by laminoplasty. We believe that survival could not have been improved had we not taken an aggressive approach.

Postoperative irradiation is generally recommended in cases of partial resection of high-grade, malignant astrocytomas and has been shown to result in increased survival and neurological improvement [15]. Even with improvements on serial MRI after complete resection of the intramedullary GBM in this patient, given the high rates of recurrence, cerebral metastasis, and leptomeningeal involvement, we performed postoperative chemoradiotherapy. We administered a focal irradiation dose of 5000 (at 200 cGy per fraction) over a period of 5 weeks, the maximum dose tolerated by the spinal cord, with concomitant temozolomide at 75 mg/m$^2$, based on our experience with intracranial GBM (6000 cGy with concurrent temozolomide 75 mg/m$^2$) [16]. Whereas a dose of 6000 cGy is used in the treatment of brain GBM, we found a dose of 5000 cGy to be safe and effective in this patient.

The feasibility of concomitant temozolomide with fractionated radiotherapy in patients with intracranial GBM has been shown in a phase III trial conducted by the European Organisation for Research and Treatment of Cancer and the National Cancer Institute of Canada [10,17]. Results showed a significant progression-free survival advantage (6.9 vs. 5 months), an overall 2-year survival advantage (27 vs. 10%), and an overall 5-year advantage (10 vs. 2%) in patients treated with this approach compared with patients treated with radiotherapy alone. We recommend continuation of adjuvant temozolomide for at least 6 months after completing concomitant radiotherapy and temozolomide treatment, as per Stupp *et al.* [10,17]. This patient did not receive adjuvant temozolomide treatment; it is possible that she would have experienced a longer progression-free survival period if this had been performed.

Epigenetic gene silencing of the *MGMT* gene by promoter methylation is associated with increased chemosensitivity, diminished DNA repair, loss of MGMT expression, and overall increased survival in patients with GBM receiving chemoradiotherapy with temozolomide [18]. The MGMT promoter methylation status in GBM tumor tissues is also known to be a predictor of pseudoprogression [19] and overall survival benefit in patients receiving radiotherapy with temozolomide [20]. However, our results showed that the MGMT promoter was unmethylated in this patient, and there was no 1p/19q loss. A randomized trial of chemoradiotherapy testing the

relationship between MGMT methylation status and survival in intracranial GBM patients had been reported. This study showed that 13.8% of the patients could survive more than 2 years even if the promoter of MGMT was unmethylated [21]. That leads to the possibility that factors other than MGMT methylation may have prolonged the survival of this patient. For example, near-complete resection of intracranial GBM was suggested to be a positive prognostic factor and has an additive effect with methylated MGMT in predicting longer survival [22]. In addition, Blough *et al.* [23] suggested that mechanisms other than methylation of the MGMT gene promoter may also induce MGMT silencing, and MGMT expression may be suppressed by methylation at the sites of promoter that have not been assayed by the investigator. Therefore, we do not recommend using the MGMT promoter assay to determine if a patient with intraspinal GBM should receive temozolomide.

In conclusion, this patient was treated aggressively, and although adjuvant temozolomide was not administered, she survived longer than average (for 33 months, of which 25 months were disease free), possibly as a result of one or more of the administered treatments, in addition to potential biological factors. Further studies are necessary to confirm the clinical significance of this treatment regimen in patients with spinal GBM.

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