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Research Article

Primary spinal glioblastoma multiforme. Single center experience and literature review

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ABSTRACT

Objectives: Spinal glioblastomas represent a rare entity accounting for ca 1–3% of all intramedullary tumors; data about survival, prognostic factors and therapeutic protocols are quite poor. Even with an aggressive multimodal management the spinal glioblastoma patients' survival remains poor, with rapid progression of the disease. This study reports our experience with the management of the primary intramedullary glioblastomas, also in regard to the current literature data.

Patients and Methods: We retrospectively analyzed the medical records of 5 patients treated at the Department for Neuro-oncology and Spine Surgery of the Clinical Center of Belgrade, Serbia, between January 2007 and December 2016 for a primary intramedullary glioblastoma. Demographic characteristics, pre-operative data and post-operative results were then compared with previous literature regarding spinal GBMs and attempt to identify potential prognostic factors.

Results: Gross total resection was achieved in two patients, while a subtotal resection was performed in the latter 3 cases; as per protocol, all patients underwent to surgery, followed by radio and chemotherapy. There were no intraoperative complications and no patients developed a new postoperative neurological defect; the median overall survival was 6 months. Progression or recurrence of disease was noted in all patients at the 3-months follow-up, despite the adjuvant treatments.

Conclusions: To the date, there is a lack of consensus on specific management of spinal glioblastomas: the extent of resection can play an important role, but it appears to be not preeminent. A shorter interval between symptoms onset and treatment and a smaller extension of the tumor seem to be correlated with better outcomes and a longer overall survival. However, there is not an adjunctive viable standardized postoperative therapy yet, which results in concrete and persistent improvement of overall survival and progression free survival.

1. Introduction

Glioblastoma multiforme (GBM) is a rare malignant entity, which represents the most frequent primary central nervous system tumor; usually, it is localized in the supratentorial space [1], whereas primary localization at cerebellum, brain stem and spinal cord is extremely rare, with a reported annual incidence of 0.12 cases out of 100,000 [2].

In particular, spinal glioblastomas represent around 7.5% of all spinal gliomas and ca 1–3% of all intramedullary tumors [3]; the most frequent localization is the cervico-thoracic tract, followed by thoracic area [1,4,5], whereas lesions at medullary conus are extremely rare [6].

Clinical presentation of spinal GBMs can be similar to other intramedullary lesions and depends on the localization and the degree of spinal cord involvement: lower limbs dysesthesia, weakness and/or

Abbreviations: GBM, glioblastoma multiforme; OS, overall survival; PFS, progression-free survival; MRI, magnetic resonance imaging; IOM, intraoperative monitoring; GTR, gross-total resection; TMZ, temozolomide; EOR, extent of resection; CHT, chemotherapy; RT, radiotherapy; SSEP, somatosensory evoked potential; MEP, motor evoked potential; D-wave, direct wave.

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muscle atrophy, along sphincters disturbances can occur at different stages. In most of the cases, the clinical conditions are rapidly progressive. In the reported literature, the overall survival ranges from 6 to 21 months [7,8,9], with mean survival of 11 months [10].

To the date, according to the rarity of data, the assessment of any prognostic factor on overall survival cannot be defined and consensus regards the specific management has not yet established. So far, treatment paradigms are based on those used for cranial GBM and include three-tier therapy [11]: surgical resection, followed by adjuvant temozolomide chemotherapy and radiotherapy. The goal of surgery, as for intracranial GBMs [12], is to achieve a maximal safe resection, being radical removal rarely possible and the role of the adjuvant chemotherapy is not frankly clear in terms of overall survival (OS) and/or progression free survival (PFS).

However, spinal GBMs, as compared to homologous intracranial lesions, harbor different genetic mutations [13] and the intramedullary localization itself constitutes an obstacle for complete surgical resection and radiotherapy planning.

Despite progress in the treatment of gliomas with the advent of aggressive multimodal management, the spinal GBM's patients' survival remains poor, with a rapid progression of the disease and unfavorable outcomes [14].

The aim of this study is to report our experience with primary intramedullary glioblastomas, also in regard to the current literature data and attempt to identify eventual prognostic factors.

2. Materials and methods

2.1. Patients data

We retrospectively analyzed the medical records of patients treated at the Department for Neuro-oncology and Spine Surgery of the Clinical Center of Belgrade, Serbia, between January 2007 to December 2016 for a primary intramedullary glioblastoma. This study was approved by the institutional review board (IRB) of the School of Medicine of the University of Belgrade (SRB), which waived the necessity for informed consent due to the retrospective nature of the study. Written informed consent was obtained from the patients prior to any invasive clinico-diagnostic or surgical procedures; consent was also obtained for the eventual publication - for scientific purposes - of any anonymous patient's records or information.

2.2. Surgical management

Gross total resection (GTR) was defined as surgical removal of at least 95% of the contrast enhancing portion of the tumor volume estimated on the preoperative MRI, while a subtotal resection (STR) was defined as <95% tumor resection.

2.3. Literature review

Data from case series of spinal primary glioblastoma, regarding adult patients, with at least 4 cases, published between 2005 and 2020 were analyzed. These results were then compared to our case series, focusing on possible prognostic factors.

3. Results

We retrospectively analyzed 5 patients medical records with the diagnosis of primary spinal glioblastoma. Demographic and clinical data are reported in Table 1.

All patients were male and the mean age at presentation was 32,4 years (range: 16–53).

Presenting symptoms were motor defects in all patients; cervicothoracic pain occurred in three cases, whilst two patients suffered also of sphincter dysfunctions.

The mean duration of symptoms was 6.4 months, the median duration of symptoms was 3 months (range: 2–12).

According to the magnetic resonance imaging (MRI) scans, these tumors appear as inhomogeneous contrast enhancing intramedullary masses with extensive perilesional edema, affecting the surrounding spinal cord [15] (Figs. 1 and 2). All patients were studied with both brain and spinal MRI: all brain MRIs didn't show any pathological alteration.

The surgical treatment was performed in all cases by the senior surgeon (DG). Patients were in a prone position under general anesthesia: laminectomy was performed in two cases, while three patients underwent a laminoplasty. Under microscopic magnification, extensive bulging of medulla was identified after dural opening. Tumor removal was run as for oncological protocol, with an intralesional debulking extending towards lesion margins. In one case, a cystic component was present, while two patients had signs of previous intralesional hemorrhage. The surgical procedures were performed under continuous intraoperative neurophysiological control using somatosensory evoked potentials (SEPs), motor evoked potentials (MEPs), and direct wave (D-wave).

Patients underwent an early postoperative spine computed tomography (CT) scan within 48 h from surgical intervention (Fig. 3). Gross total resection (GTR), was achieved in two patients, while a subtotal resection (STR), was performed in the latter 3 cases. The lesion was located in the cervical spine in one patient, in the cervicothoracic tract in two patients, in the thoracic medulla in two cases: the tumor extent ranged from 2 to 8 levels.

There were no intraoperative mortality or complications, and no patient developed a new postoperative neurological deficit. One patient had a transitory drop of the evoked potentials, with no change in the D-wave: in this case, considering the wide infiltration of the tumor, affecting almost the totality of the spinal cord section at that level, the surgical resection was stopped, in order to preserve the remaining neurological functions.

All patients were presented to our institutional tumor board and therefore the management of each case was tailored within such a multidisciplinary team. All patients were planned for postoperative irradiation and chemotherapy around 1 month after surgery; however three patients couldn't start or complete the planned adjuvant therapy because of early progression of the disease; 2 cases completed the

Table 1
Demographical and clinical characteristics. GMS: grade motor scale.

	Gender	Age	Symptoms	Urinary control	Localization	Motor function
Patient 1	male	16	3 months of back pain, leg weakness, incontinence	No	T9-T12	Lower limbs GMS 2
Patient 2	male	39	12 months of left arm and leg weakness	Yes	C7-T1	left leg and hand GMS 3
Patient 3	male	33	2 months of back pain and leg weakness	Yes	T2-T4	Right leg GMS 3 left leg GMS 2
Patient 4	male	53	12 months of cervical pain and recent onset of quadriparesis	No	Craniocervical-C7	Right arm GMS 1 left arm GMS 3 legs GMS 2
Patient 5	male	21	3 months of quadriparesis and ataxia	Yes	C3-T1	GMS 4 for all extremities except left arm GMS 3

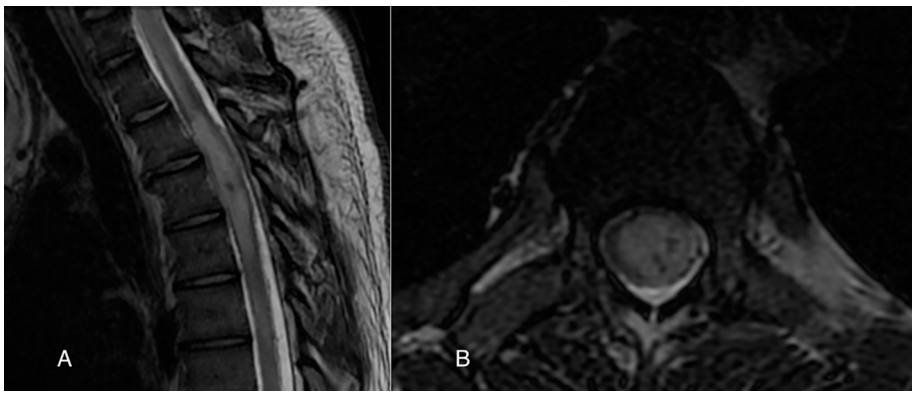

Fig. 1. Patient 3 preoperative images: Sagittal (A) and axial (B) T2-weighted spinal MRI show inhomogeneous thoracic intramedullary mass with perilesional edema.

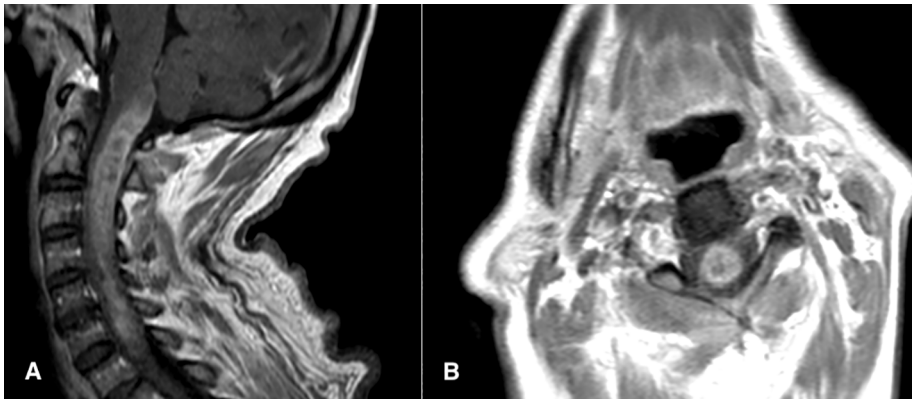

Fig. 2. Patient 4 preoperative images: Sagittal (A) and axial (B) post-contrast T1 spinal MRI demonstrate an invasive cervical lesion, from C0 to C7 with inhomogeneous contrast enhancement.

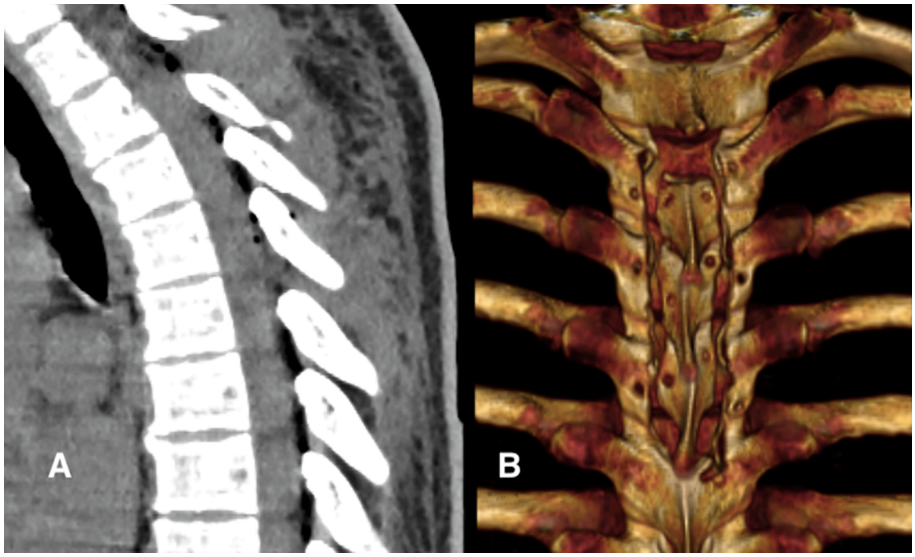

Fig. 3. Patient 3 early postoperative images: (A) spinal CT scan shows the resection of the tumor without any complications; (B) the 3D reconstruction reveals the laminotomy's levels.

adjuvant radiotherapy treatment with a radiation dose of 50,4 Gy in 28 daily fractions. The individual treatments are reported in Table 2.

In our series the mean overall survival was 6 months with a median OS of 5 months. Progression or recurrence of disease was noted in all patients at the 3-months follow-up, despite the adjuvant treatments.

4. Discussion

Spinal glioblastomas represent very rare malignant nervous system tumors with an overall survival reported between 6 and 21 months [8] as related to the severe and progressive neurological impairment and the poor prognosis; besides, multimodality aggressive treatment approach

Table 2
Treatment characteristics and follow up. NE: neurological examination; RT: radiotherapy; CHT: chemotherapy; OS: overall survival.

	Surgical technique	Grade of resection	Postop NE	RT	CHT	OS
Patient 1	laminectomy,	total	Slight worsening	yes	PCV, III cycles	11 months
Patient 2	laminectomy,	subtotal	stable	25, 2 Gy interrupted	no	5 months
Patient 3	laminoplasty,	subtotal	intraop drop of MEP stable	yes	temozolomide	5 months
Patient 4	Laminoplasty	subtotal	Slight worsened	no	no	3 months
Patient 5	Laminoplasty	total	improvement	RT, 4,8 Gy 3 fractions, interrupted	no	6 months

seems to not affect the natural course of the disease [3,16].

Cheng et al. [17] found that the combination of postoperative radiotherapy and temozolomide can improve prognosis in these patients, albeit a median OS of 15 months was noted. As well, Liu et al [3] reported an OS of 20 months, but despite adjuvant treatments only one patient showed postoperative neurological status improvement.

Indeed, according to the literature review of Konar et al [4], based on 128 patients selected from 58 published articles, median OS of 11 months was observed. Moreover, the majority of patients complained of a low quality of life; they present severe disability at the time of diagnosis, with low possibilities of neurological improvement [14]. An early diagnosis and a precocious treatment it's mandatory to promote an improvement of OS, with preservation of quality of life.

In our study, we retrospectively analyzed the medical records of 5 patients treated between January 2007 and December 2016 for an intramedullary glioblastoma and our results are consistent with the data reported in the literature [14,18] (Table 3).

Unfortunately, all patients of our series were young men with a mean age at the time of diagnosis of 32,4 years. Nevertheless, we confirmed that age and sex do not affect prognosis as reported in an integrative survival analysis by Konar et al. [18].

In our series, the most frequent localization for spinal GBMs was the cervico-thoracic and thoracic tract (in 4 of 5 patients, 80%). According to Raco et al. [11], cervical glioblastomas appear to be the most unfavorable due to increased morbidity associated with the involvement of the higher cervical areas (respiratory insufficiency appears at an earlier stage) and the eventual post-operative cervical instability. The only one patient with a cervical localization of the present series showed the poorest OS (3 months), if compared to the other cases that showed a mean OS of 6–7 months. Accordingly, related symptoms are leg weakness with or without muscle atrophy, dysesthesia and/or bladder-bowel disturbances and usually have a rapid progression [7,20].

In all our patients the presenting symptoms were leg weakness and back pain. This unspecific clinical onset can be pointed out as a possible reason of late diagnosis [6,21]: two of our patients indeed had symptoms since 12 months prior than diagnosis and mean OS was 4 months, even inferior to median OS of our series, i.e. 5 months. Considering GBM inner progression rate, it does not seem surprising that our median OS rate is inferior also to the overall survival range reported for spinal GBMs in the literature [22,23,24] confirming that diagnostic delay can tremendously affect the outcomes.

Concerning the treatment, the goal of surgery for spinal GBMs is to obtain the highest resection rate, avoiding damages; however, in spinal GBMs surgery, as for infiltrative growth pattern, a total resection and especially supra-total resection [25] can be difficult to achieve and eventually it is associated with an high morbidity rates [26,27]. Hence, the use of electrophysiological IOM is mandatory. We observed that the D-wave demonstrated a statistically significant higher ability to predict postoperative damages as compared with SSEPs and MEPs alone [28] and allowed the surgeon to safely proceed with dissection and removal maneuvers [29]; accordingly, resection was stopped at the external margin of edematous medulla or in case of pathologic changes in the evoked motor potentials (D-wave) [30]. Sala et al [31] compared the neurological outcomes of 50 patients operated with the assistance of intraoperative monitoring (IOM) (SEPs, mMEPs, and D-wave) with 50 patients, operated by the same team, without IOM: monitoring protocol significantly improved motor outcomes at a follow-up of at least 3 months, being useful even in those patients with severe neurological defects.

We adopted IOM in all procedures obtaining good rate of extent of resection (EOR) (GTR 40%, 2 out of 5 patients), without post-operative neurological deficits, resulting in longer mean OS (8.5 months) and better quality of life.

Several studies pointed out that the extent of resection does not appear to be a reliable prognostic factor for overall survival in spinal GBMs [22,32,33] and, as reported by Behmanesh [14] and Konar [18], extensive surgical manipulation can facilitate tumor cell seeding and dissemination. Also, in our series, extent of surgical resection did not influence the length of survival; rather we noted that patients with a lesser degree of tissue involvement had a better prognosis. Patient 1, 2

Table 3
Literature data compared with our series. C/T: cervical/thoracic; GTR: gross-total resection; M/F: Male/Female; CHT chemotherapy; RT: radiotherapy; OS: overall survival; NA: not available.

	Median age (years)	N° of patients	Median symptoms duration (months)	Tumor location C/T	GTR	Sex M/F	CHT	RT	Median OS (months)
Liu et al. [3] 2015	31	5	5	2/3	60%	5/0	2 TMZ	3	20
Cheng et al. [17] 2017	28	14	NA	4/10	28,6%	8/6	9 TMZ	9	15
Raco et al. [11] 2005	33	12	NA	7/5	25%	7/5	5 TMZ	8	17
Seki et al. [19] 2015	30	4	4	1/3	0%	3/1	2 TMZ	4	12,5
Yanamadala et al. [42] 2016	40	6	NA	3/3	0%	2/4	3 TMZ	3	18
Behmanesh et al. [14] 2017	43	4	NA	2/2	0%	0/4	1 TMZ + Bevacizumab 1 TMZ 1 TMZ + CCNU + Etoposide 1 TMZ + Rapamycin + Sunitinib	4	30
Our spinal series	33	5	3	1/4	40%	5/0	1 TMZ 1 PCV	4	5

and 3 who presented smaller lesions (4, 2 and 3 levels involvement respectively) presented a longer OS, whilst patient with a wider lesion (8 levels) had the poorest OS (3 months). It can be assumed that lesions with a limited dimension are at an initial stage, so the treatment with surgery and adjuvant therapies can be more effective. Besides, the intraoperative dissemination risk and surgery complications rate are lower.

Focusing on the possible limitations of our study, our median OS seemed to be shorter than the other reported in the literature [34,35,36]. This could be probably due to the diagnostic delay (two patients had symptoms for 12 months before the diagnosis): patients presented with extended lesions and with a severe clinical condition; these aspects resulted in a lower probability of complete surgical resection and limited time for adjuvant therapies. Moreover, one of the major limitations of our study is the lack of molecular characterization of GBMs, such as IDH type and MGMT status. These cases have been treated in Serbia where this kind of tests were not available routinely in public hospitals.

Finally, it is worth underlining that a standardized adjuvant treatment protocol has not been yet established [37]: for spine tumors, the radiation protocol requires application of 50,4 Gy in 28 daily fractions, which is a lower dose as compared to brain radiotherapy (60 Gy). This is due to the spinal cord sensitivity to higher radiation doses, resulting in permanent injuries and neurological deterioration [38]. Spinal gliomas are considered not radiosensitive tumors [39], so their rapid local progression might be the underdosage of the radiation treatment.

Concerning chemotherapy, its role on medullary gliomas has not been clarified yet: Kim et al. [40] found that treatment with temozolomide during and after radiation therapy might provide survival benefit to patients with primary spinal cord GBM. Several studies [41,42] reported positive results with the use of Bevacizumab for chemotherapy in addition to temozolimide (TMZ), per its effect of decreasing peritumoral edema and mass effect.

Temozolomide was introduced in Serbia in 2010 as standard adjuvant treatment for brain gliomas, but only one patient of the present series received TMZ adjuvant treatment.

In our series, only two patients had the chance to start and complete a CHT cycle, patient 1 with PCV and patient 3 with TMZ, respectively. Focusing on their OS, patient 1 who had a total resection showed a longer OS (11 months VS 5 months). Nevertheless, the limited number of cases doesn't permit to formulate any other conclusion.

5. Conclusions

Primary intramedullary glioblastomas represent a rare entity, who's rapid progression results in fatal outcomes despite aggressive treatment. To the date, there is a lack of consensus on specific management of spinal GBMs: the extent of resection can play an important role, but it appears to be not preeminent. A shorter interval between symptoms onset and treatment and a smaller extension of the tumor seem to be correlated with better outcomes and a longer OS. However, there is not an adjunctive viable standardized postoperative therapy yet, which results in concrete and persistent improvement of OS and/or PFS. Further studies on wider series are attended to identify new strategies leading to better outcomes.

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Informed consent

This study was approved by the institutional review board (IRB) of the School of Medicine of the University of Belgrade (SRB), which waived the necessity for informed consent due to the retrospective nature of the study.

Conflict of interest

There is no conflict of interest to disclose.

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References

[1] B. Guidetti, S. Mercuri, R. Vagnozzi, Long-term results of the surgical treatment of 129 intramedullary spinal gliomas, J. Neurosurg. 54 (3) (1981) 323–330.
[2] J. Liu, M. Zheng, W. Yang, S.L. Lo, J. Huang, Impact of surgery and radiation therapy on spinal high-grade gliomas: a population-based study, J. Neurooncol. 139 (3) (2018) 609–616.
[3] A. Liu, E.W. Sankey, C. Bettegowda, P.C. Burger, G.I. Jallo, M.L. Groves, Poor prognosis despite aggressive treatment in adults with intramedullary spinal cord glioblastoma, J. Clin. Neurosci. 22 (10) (2015) 1628–1631.
[4] S.K. Konar, S.C. Bir, T.K. Maiti, A. Nanda, A systematic review of overall survival in pediatric primary glioblastoma multiforme of the spinal cord, J. Neurosurg. Pediatr. 19 (2) (2017) 239–248.
[5] F.J. Epstein, J.P. Farmer, D. Freed, Adult intramedullary astrocytomas of the spinal cord, J. Neurosurg. 77 (3) (1992) 355–359.
[6] W.C. Choi, J.H. Lee, S.H. Lee, Spinal cord glioblastoma multiforme of conus medullaris masquerading as high lumbar disk herniation, Surg. Neurol. 71 (2) (2009) 234–237, discussion 237.
[7] N. Morais, L. Mascarenhas, J.P. Soares-Fernandes, A. Silva, Z. Magalhães, J. A. Costa, Primary spinal glioblastoma: a case report and review of the literature, Oncol. Lett. 5 (3) (2013) 992–996.
[8] H. Adams, J. Avendaño, S.M. Raza, Z.L. Gokaslan, G.I. Jallo, A. Quiñones-Hinojosa, Prognostic factors and survival in primary malignant astrocytomas of the spinal cord: a population-based analysis from 1973 to 2007, Spine (Phila Pa 1976) 37 (12) (2012) E727-35.
[9] M. Santi, H. Mena, K. Wong, K. Koeller, C. Olsen, E.J. Rushing, Spinal cord malignant astrocytomas. Clinicopathologic features in 36 cases, Cancer 98 (3) (2003) 554–561.
[10] R. Stupp, W.P. Mason, M.J. van den Bent, M. Weller, B. Fisher, M.J.B. Taphoorn, K. Belanger, A.A. Brandes, C. Marosi, U. Bogdahn, J. Curschmann, R.C. Janzer, S. K. Ludwin, T. Gorlia, A. Allgeier, D. Lacombe, J.G. Cairncross, E. Eisenhauer, R. O. Mirimanoff, Group, Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma, N. Engl. J. Med. 352 (10) (2005) 987–996.
[11] A. Raco, V. Esposito, J. Lenzi, M. Piccirilli, R. Delfini, G. Cantore, Long-term follow-up of intramedullary spinal cord tumors: a series of 202 cases, Neurosurgery 56 (5) (2005) 972-81; discussion 972-81.
[12] R. Illic, T. Somma, D. Savic, F. Frio, M. Milicevic, D. Solari, M. Nikitovic, S. Lavrnic, S. Raicevic, S. Milosevic, L.M. Cavallo, P. Cappabianca, D. Grujicic, A Survival Analysis with Identification of Prognostic Factors in a Series of 110 Patients with Newly Diagnosed Glioblastoma Before and After Introduction of the Stupp Regimen: A Single-Center Observational Study, World Neurosurg. 104 (2017) 581–588.
[13] J. Shows, C. Marshall, A. Perry, B.K. Kleinschmidt-DeMasters, Genetics of Glioblastomas in Rare Anatomical Locations: Spinal Cord and Optic Nerve, Brain Pathol. 26 (1) (2016) 120–123.
[14] B. Behmanesh, M. Setzer, J. Konczalla, P. Harter, J. Quick-Weller, L. Imoehl, K. Franz, F. Gessler, V. Seifert, G. Marquardt, Management of Patients with Primary Intramedullary Spinal Cord Glioblastoma, World Neurosurg. 98 (2017) 198–202.
[15] G. Sze, G. Krol, R.D. Zimmerman, M.D. Deck, Intramedullary disease of the spine: diagnosis using gadolinium-DTPA-enhanced MR imaging, AJR Am. J. Roentgenol. 151 (6) (1988) 1193–1204.
[16] E. Caro-Osorio, J.C. Herrera-Castro, A. Barbosa-Quintana, M. Benvenutti-Regato, Primary Spinal Cord Small-Cell Glioblastoma: Case Report and Literature Review, World Neurosurg. 118 (2018) 69–70.
[17] X. Cheng, S. Lou, S. Huang, H. Chen, J. Liu, Primary Spinal Cord Glioblastoma Multiforme: A Retrospective Study of Patients at a Single Institution, World Neurosurg. 106 (2017) 113–119.
[18] S.K. Konar, T.K. Maiti, S.C. Bir, P. Kalakoti, P. Bollam, A. Nanda, Predictive Factors Determining the Overall Outcome of Primary Spinal Glioblastoma Multiforme: An Integrative Survival Analysis, World Neurosurg. 86 (2016) 341–348.e3.
[19] T. Seki, K. Hida, S. Yano, T. Aoyama, I. Koyanagi, K. Houkin, Surgical Outcomes of High-Grade Spinal Cord Gliomas, Asian Spine J. 9 (6) (2015) 935–941.
[20] A. Chanchotisatien, J. Xiong, J. Yu, S. Chu, Exophytic Primary Intramedullary Spinal Cord Glioblastoma: Case Report and Critical Review of Literature, World Neurosurg. 122 (2019) 573–576.
[21] P.K. Singh, V.K. Singh, J. Tomar, A. Azam, S. Gupta, S. Kumar, Spinal glioblastoma multiforme: unusual cause of post-traumatic tetraparesis, J. Spinal Cord Med. 32 (5) (2009) 583–586.

[22] S. Lam, Y. Lin, S. Melkonian, Analysis of risk factors and survival in pediatric high-grade spinal cord astrocytoma: a population-based study, Pediatr. Neurosurg. 48 (5) (2012) 299–305.
[23] P. Banczerowski, M. Simó, L. Sipos, F. Slowik, G. Benoist, R. Veres, Primary intramedullary glioblastoma multiforme of the spinal cord: report of eight cases, Ideggyogy Sz 56 (1–2) (2003) 28–32.
[24] T.S. Gee, A.R. Ghani, B. Idris, M.S. Awang, Case report: a rare case of pediatric conus medularis glioblastoma multiforme, Med. J. Malaysia 67 (4) (2012) 438–441.
[25] S.L. Hervey-Jumper, M.S. Berger, Evidence for Improving Outcome Through Extent of Resection, Neurosurg. Clin. N Am. 30 (1) (2019) 85–93.
[26] B. Wolff, A. Ng, D. Roth, K. Parthey, M. Warmuth-Metz, M. Eyrich, U. Kordes, R. Kortmann, T. Pietsch, C. Kramm, J.E. Wolff, Pediatric high grade glioma of the spinal cord: results of the HIT-GBM database, J. Neurooncol. 107 (1) (2012) 139–146.
[27] A.R. Cohen, J.H. Wisoff, J.C. Allen, F. Epstein, Malignant astrocytomas of the spinal cord, J. Neurosurg. 70 (1) (1989) 50–54.
[28] R. Ghadirpour, D. Nasi, C. Iaccarino, A. Romano, L. Motti, R. Sabadini, F. Valzania, F. Servadei, Intraoperative neurophysiological monitoring for intradural extramedullary spinal tumors: predictive value and relevance of D-wave amplitude on surgical outcome during a 10-year experience, J. Neurosurg. Spine 30 (2) (2018) 259–267.
[29] A. Scibilia, G. Raffa, V. Rizzo, A. Quartarone, M. Visocchi, A. Germanò, F. Tomasello, Intraoperative Neurophysiological Monitoring in Spine Surgery: A Significant Tool for Neuronal Protection and Functional Restoration, Acta Neurochir. Suppl. 124 (2017) 263–270.
[30] M.O. Kelleher, G. Tan, R. Sarjeant, M.G. Fehlings, Predictive value of intraoperative neurophysiological monitoring during cervical spine surgery: a prospective analysis of 1055 consecutive patients, J. Neurosurg. Spine 8 (3) (2008) 215–221.
[31] F. Sala, A. Bricolo, F. Faccioli, P. Lanteri, M. Gerosa, Surgery for intramedullary spinal cord tumors: the role of intraoperative (neurophysiological) monitoring, Eur. Spine J. 16 (S2) (2007) 130–139.
[32] M.J. McGirt, I.M. Goldstein, K.L. Chaichana, M.E. Tobias, K.F. Kothbauer, G.I. Jallo, Extent of surgical resection of malignant astrocytomas of the spinal cord: outcome analysis of 35 patients, Neurosurgery 63 (1) (2008) 55-60; discussion 60-1.
[33] H.M. Sandler, S.M. Papadopoulos, A.F. Thornton, D.A. Ross, Spinal cord astrocytomas: results of therapy, Neurosurgery 30 (4) (1992) 490–493.
[34] J.J. Timmons, K. Zhang, J. Fong, E. Lok, K.D. Swanson, S. Gautam, E.T. Wong, Literature Review of Spinal Cord Glioblastoma, Am. J. Clin. Oncol. 41 (12) (2018) 1281–1287.
[35] C.-X. Shen, J.-F. Wu, W. Zhao, Z.-W. Cai, R.-Z. Cai, C.-M. Chen, Primary spinal glioblastoma multiforme: A case report and review of the literature, Medicine (Baltimore) 96 (16) (2017) e6634, https://doi.org/10.1097/MD.0000000000006634.
[36] M.T. Milano, M.D. Johnson, J. Sul, N.A. Mohile, D.N. Korones, P. Okunieff, K. A. Walter, Primary spinal cord glioma: a Surveillance, Epidemiology, and End Results database study, J. Neurooncol. 98 (1) (2010) 83–92.
[37] F.M. Moinuddin, M.A. Alvi, P. Kerezoudis, W. Wahood, J. Meyer, D.H. Lachance, M. Bydon, Variation in management of spinal gliobastoma multiforme: results from a national cancer registry, J. Neurooncol. 141 (2) (2019) 441–447.
[38] J.P. Kirkpatrick, A.J. van der Kogel, T.E. Schultheiss, Radiation dose-volume effects in the spinal cord, Int. J. Radiat. Oncol. Biol. Phys. 76 (3) (2010) S42–S49.
[39] X. Han, X. Xue, H. Zhou, G.e. Zhang, A molecular view of the radioresistance of gliomas, Oncotarget 8 (59) (2017) 100931–100941.
[40] W.H. Kim, S.H. Yoon, C.Y. Kim, K.J. Kim, M.M. Lee, G. Choe, I.A. Kim, J.H. Kim, Y. J. Kim, H.J. Kim, Temozolomide for malignant primary spinal cord glioma: an experience of six cases and a literature review, J. Neurooncol. 101 (2) (2011) 247–254.
[41] T.J. Kaley, I. Mondesire-Crump, I.T. Gavrilovic, Temozolomide or bevacizumab for spinal cord high-grade gliomas, J. Neurooncol. 109 (2) (2012) 385–389.
[42] V. Yanamadala, R.M. Koffie, G.M. Shankar, J.I. Kumar, Q.D. Buchlak, V. Puthenpura, M.P. Frosch, T.M. Gudewicz, L.F. Borges, J.H. Shin, Spinal cord glioblastoma: 25years of experience from a single institution, J. Clin. Neurosci. 27 (2016) 138–141.