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PRIMARY SPINAL CORD GLIOBLASTOMA AN INSTITUTIONAL EXPERIENCE AND REVIEW OF LITERATURE

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ABSTRACT

BACKGROUND: Primary spinal cord glioblastoma multiforme (GBM) is a rare clinical entity and prognosis is very poor. Investigation of choice is MRI and the standard treatment is surgery with maximal safe resection followed by adjuvant radiotherapy and chemotherapy. Several studies show that even after such aggressive treatments, the estimated median survival is around 15 months. Our study reports institutional experience and management of four patients with primary spinal GBM who received treatment in our institute from 2018 to2024. All patients succumbed due to illness.

MATERIAL AND METHOD: We analysed the medical records of all patients retrospectively treated at the Department of the Neurosurgery, Mahatma Gandhi Hospital and Medical College Jaipur INDIA, between May 2018 and December 2023 for primary Spinal intramedullary glioblastoma and we found only 4 patients. Pre-operative data and post-operative results demographic characteristics, were then compared with previous literature regarding spinal GBMs and attempt to identify the related factors.

RESULTS: Subtotal resection was achieved in three patients, while a gross total resection was performed in one case; as per protocol all patients underwent surgery followed by radiotherapy and chemotherapy. No significant intraoperative complications or newer postoperative neurological deficit developed; the median overall survival was 11 months. Progression or recurrence of disease was noted in all patients at the 3-months follow-up despite the adjuvant treatments.

CONCLUSIONS: Till now, there is no fixed protocol regarding specific management of spinal glioblastomas: the extent of resection can play an important role but it appears to be insignificant pertaining to long survival. Time interval between the onset of symptoms and treatment and a smaller extension of the lesion seem to be correlated with better outcomes and increase 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.

KEYWORDS: Primary Spinal Cord Tumor, Spinal Glioblastoma, Intramedullary GBM

ABBREVIATIONS

GBM-glioblastoma multiforme, OS-overall survival, PFS-progression-free survival, MRI -magnetic resonance imaging, GTR-gross-total resection, TMZ -temozolomide, EOR-extent of resection RT-radiotherapy, CSF-Cerebro Spinal Fluid.

INTRODUCTION

Astrocytoma is the most common tumor of the central nervous system. (1) Spinal cord astrocytomas are rare, making up about 1% of all primary central nervous system tumors and 6-8% of all spinal cord tumors (2). Glioblastomas (GBMs) account for approximately 7.5% of all intramedullary gliomas and 1-3% of all spinal cord tumors. (3,4) Notably, more than 60% of GBMs develop in the cervicothoracic region, (1,5,6, 7) with the cervical area being the most frequent localization followed by the thoracic area, (8, 9, 10) while lesions at the medullary conus are extremely rare. (11)

Clinically, spinal GBMs present similarly to other intramedullary lesions, with symptoms depending on the location and extent of spinal cord involvement. These symptoms can include neck and back pain, lower limb dysesthesia, weakness, muscle atrophy, and bowel and bladder disturbances, often progressing rapidly. Reported literature indicates overall survival ranges from 6 to 21 months, (12,13,14) with a mean survival of 15 months. (15)

Due to the rarity of data, it is challenging to define any prognostic factors for overall survival, and there is no consensus on specific management strategies. Treatment protocols typically follow those used for cranial GBMs, involving a three-tier approach of surgical resection, (16) followed by adjuvant chemotherapy (temozolomide) and radiotherapy. The goal of surgery is to achieve maximal safe resection, but radical removal is rarely possible, and the role of adjuvant chemotherapy in terms of overall survival and progression-free survival remains unclear. (17)

Spinal GBMs differ from intracranial GBMs in terms of genetic mutations, (18) and their intramedullary location poses challenges for complete surgical resection and radiotherapy planning. Despite advances in aggressive multimodal management for gliomas, survival for spinal GBM patients remains poor, with rapid disease progression and unfavourable outcomes. (19)

This study aims to report our institutional experience with primary spinal intramedullary glioblastomas, focusing on management and attempting to identify potential prognostic factors.

MATERIAL AND METHOD

We analysed the medical records of all patients retrospectively, that treated at the Department of the Neurosurgery Mahatma Gandhi Hospital and Medical College Jaipur India between May 2018 and December 2023 for primary Spinal intramedullary glioblastoma and we found 4 patients Ethics committee of Mahatma Gandhi Medical College approved this study.

RADIOLOGY

Preoperative MRI of these patients indicated an intramedullary lesion in the cervical cord, extending from the cervicomedullary junction to the cervicothoracic region, causing cord expansion (fig-1). Although the specific levels varied slightly between patients, the majority of the lesion was located in the cervical region. The lesion was centrally located, showing heterogeneous contrast enhancement (fig-2), with areas of hemorrhage in two patients. There was also associated non-enhancing T2W hyperintensity in the adjacent cord parenchyma, likely representing edema. The differential diagnosis

included ependymoma and astrocytoma. Within three days of admission and provisional diagnosis, the patient underwent surgery.

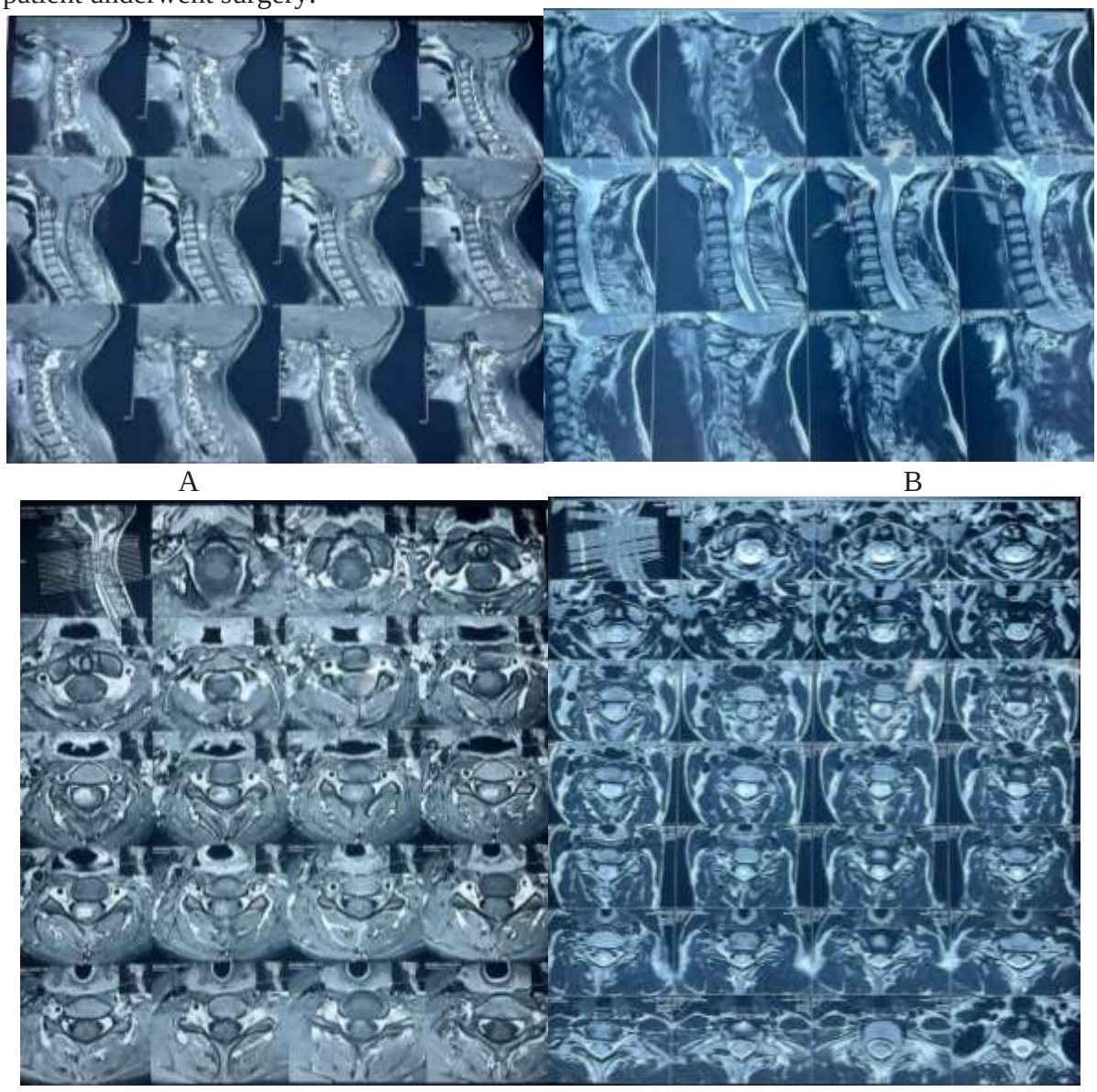


Figure 1. MRI Cervical spine (A) T1 with contrast image sagittal section (B) T2w image sagittal section (C) T1 with contrast axial section (D) T2w image axial section. Image suggestive of tumor extending from cervicomedullary junction to C6-7 level with contrast enhancement at the level of C3-4 (A) lesion expanding the cord with surrounding edema (B) enhancing tumor present in the centre of cord with slightly more on right side(C), expanded cord with compromised canal (D)

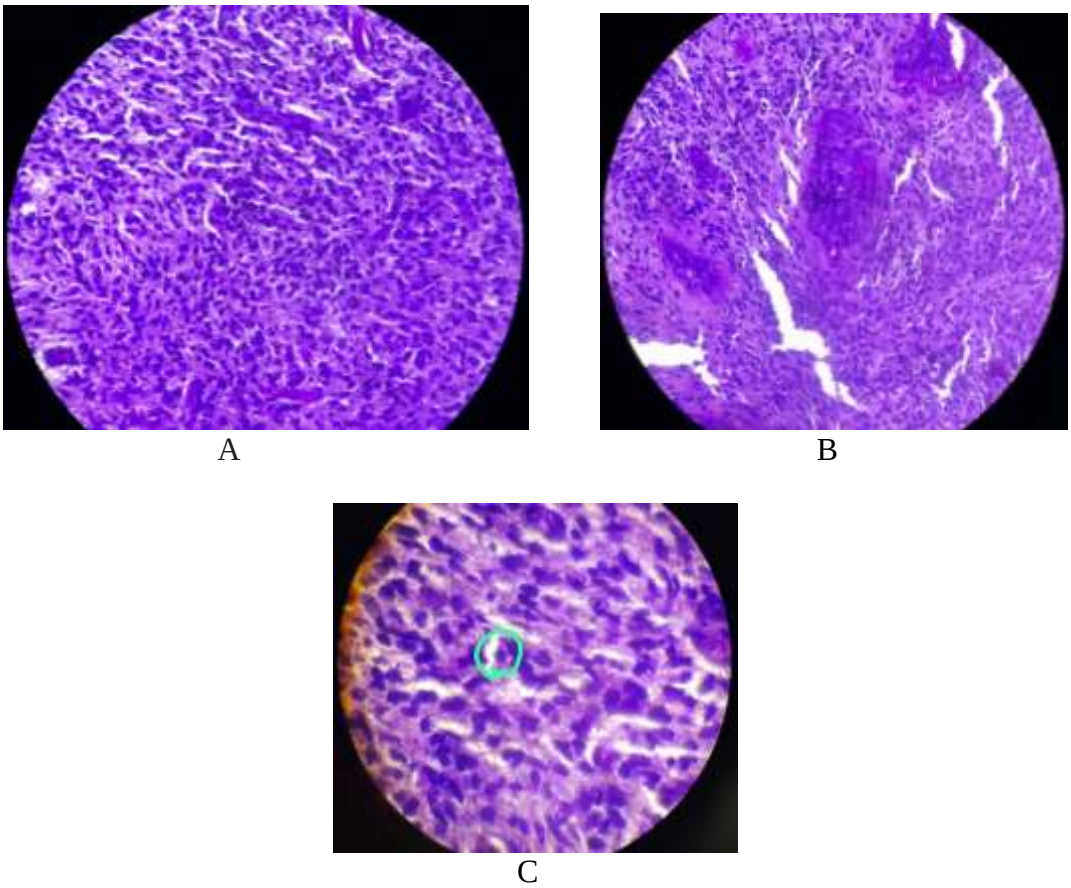
SURGICAL MANAGEMENT

Gross total resection (GTR) is defined as the surgical removal of more than 95% of the contrast-enhancing portion of the tumor volume as estimated on the preoperative MRI, while subtotal resection (STR) is defined as the removal of less than 95% of the tumor. All patients underwent surgical treatment. They were operated on in the prone position under general anesthesia, with continuous intraoperative neurophysiological monitoring using somatosensory evoked potentials (SEPs) and motor evoked potentials (MEPs). A laminectomy was performed in each case, and using a high-end microscope, a midline dural opening was made. Extensive bulging of the cord tissue due to the tumor and surrounding edema was observed. A midline corticectomy was performed, and tumor removal was done in a piecemeal fashion, as there was no well-defined surgical plane between the tumor and spinal cord tissue in any case. Initial intralesional debulking was performed from the central part of

the tumor, extending towards the periphery. GTR was achieved in one case, while STR was performed in the remaining three cases.

HISTOPATHOLOGICAL AND MOLECULAR FEATURES

The histopathology report indicated a high-grade diffuse glioma composed of neoplastic astrocytes with nuclear atypia in a fibrillary microcystic background. The blood vessels exhibited microvascular endothelial glomeruloid proliferation with areas of necrosis and hemorrhage, and significant mitotic activity was observed in all cases. Immunohistochemistry for Isocitrate Dehydrogenase 1 (IDH1) mutation was negative in three cases and positive in one case. ATRX showed intact nuclear expression, and p53 expression demonstrated strong nuclear positivity. These histopathological and molecular findings are suggestive of Glioblastoma (WHO Grade IV).



A B C

Figure 2 Microscopic images of spinal glioblastoma, haematoxylin and eosin stain; A -Increase cellular Pleomorphism B- Increase Endothelial Proliferation C - Increase mitotic activity

RESULTS

We retrospectively analysed 4 patients medical record with the diagnosis of primary spinal glioblastoma. Demographic and clinical data are reported in Table 1.

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

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Gender	Female	Female	Male	Female
Age	13	43	48	38
Symptoms	10 days of Quadriparesis, Leg pain, neck pain	3 months of B/L limb weakness numbness left arm and leg	One and half month neck pain and Quadriparesis	3 months of quadriparesis and neck pain, paraesthesia left lower limb

Bowel/ Bladder	Normal	Normal	Yes	Yes
Localization	C2-C6	C2-C7	C4-D1	C3-T1
Motor function	B/L LL 2/5	Rt side 2/5, Lt side 1/5	Left side Both U/Land L/L 3/5Rt side 2/5	GMS 4 for all extremities except left arm GMS 3
Extent of resection GTR/STR	GTR	STR	STR	STR
Overall survival (OS) in month	9	15	18	13

In our study, most patients were young, with 75% being female and a mean age of 35.5 years (range: 13–48). All patients presented with motor deficits, and three experienced neck pain, while two also had sphincter dysfunctions. The average duration of symptoms was 59 days (approximately 2 months), with a shorter duration of symptoms being associated with a very poor prognosis.
Microscopic intraoperative findings indicated that the tumor was heterogeneous in appearance, slightly yellowish-grey, vascular, suckable, and with ill-defined margins, making it challenging to distinguish between tumor tissue and normal spinal cord. A cystic component was present in one case, one patient showed signs of previous hemorrhage, and three patients had discrete necrotic tissue.
In the postoperative period, there was slight improvement in neurological functions in two cases, followed by gradual deterioration in all cases. Histopathological studies confirmed primary spinal GBM, and after confirmation, adjuvant radiotherapy was administered alongside concurrent chemotherapy with temozolomide. During the follow-up period, the clinical condition initially showed slight improvement but then gradually worsened.
Postoperative MRI was performed within 48 hours of surgery, with subsequent imaging at 3 and 6 months. Gross total resection (GTR) was achieved in one patient, while subtotal resection (STR) was performed in the other three cases. The lesion was located in the cervical spine in three patients and in the cervicothoracic tract in one patient, with tumor extent ranging from 2 to 6 levels.

LITERATURE REVIEW

We reviewed data from multiple case series of adult patients with spinal primary glioblastoma, each involving at least four cases, published between 2005 and 2020. We then compared these findings to our own case series to identify potential prognostic factors.

Table 2. Literature data compared with our series.

	Median age (years)	**N° of patient**	**Median symptoms duration (months)**	**Tumor location C/T**	**GTR**	**Sex M/F**	**CHT**	**RT**	**Median OS (months)**
Liu et al [26] 2015	31	5	5	2/3	60%	5/0	2 TMZ	3	20
Cheng et al [25] 2017	28	14	NA	4/10	28,6 %	8/6	9 TMZ	9	15

Raco et al [19] 2005	33	12	NA	7/5	25%	7/5	5 TMZ	8	17
Seki et al [27] 2015	30	4	4	1/3	0%	3/1	2 TMZ	4	12.5
Yanamadala et al [17] 2016	40	6	NA	3/3	0%	2/4	3 TMZ	3	18
Behmanesh et al [8] 2017	43	4	NA	2/2	0%	0/4	1 TMZ+Bevacizumab 1 TMZ 1 TMZ+CCNU+Etoposide 1 TMZ+Rapamycin+Sunitinib	4	30
Jokovic et. Al [21]	33	5	3	1/4	40%	5/0	1 TMZ 1 PCV	4	5
Our study	35	4	2	3/1	25%	1/3	3 TMZ	6	11

C/T: cervical/thoracic; GTR: gross-total resection; M/F: Male/Female; CHT chemotherapy; RT: radiotherapy; OS: overall survival; NA: not available.

DISCUSSION

Primary spinal cord glioblastoma is a rare condition. Most patients present at a young age, with the mean age of presentation varying between 26 and 40 years across different studies, and 35.5 years in our study. While most studies indicate a male predominance, (9,10,13) our study found a higher incidence in females. A 2021 study by Jokovic M. et al, which retrospectively analyzed medical records of five patients, confirmed that age and sex do not affect prognosis. (21)

The thoracic and cervical regions of the spinal cord are most commonly affected, followed by the cervicothoracic area, lumbar region, and conus medullaris. (16). Jokovic et al. [21] noted that the cervicothoracic and thoracic regions are the most common sites for spinal GBMs. In our study, all cases had tumors in the cervical region, with one extending to the cervicothoracic region, which appears to be a poor prognostic factor compared to other locations. According to Raco et al. [19], cervical glioblastomas are particularly unfavorable due to increased morbidity associated with higher cervical area involvement, leading to earlier respiratory insufficiency and potential postoperative cervical instability.

Clinical symptoms of primary spinal GBM typically include leg weakness with or without muscle atrophy, dysesthesia, and/or bladder-bowel disturbances, often progressing rapidly [7,20]. The most common presentation involves motor weakness, neck and back pain, and sensory deficits, sometimes accompanied by bladder and bowel disturbances. (9) In our study, all patients initially presented with neck pain and paresis that quickly progressed to plegia, with sensory symptoms primarily affecting the lower limbs in a nonspecific dermatomal pattern.

Primary spinal glioblastoma multiforme (GBM) typically has a grim prognosis and a high mortality rate, comparable to that of intracranial GBM. Complications associated with this condition can include the spread of cancer to the brain, hydrocephalus caused by cerebrospinal fluid dissemination, progression of the tumor, and paralysis affecting the respiratory system. (9,12) In our study, no space-occupying lesions were detected in the brain. While approximately 25% of intracranial glioblastoma cases can seed to the spinal cord, the reverse seeding from spinal to intracranial locations

is rare. (1,2) Spinal glioblastoma is thought to spread through the leptomeningeal pathway. (4,1) Intracranial metastases are generally found in the ventricles, brainstem, subarachnoid space, hypothalamus, thalamus, cerebellum, and septum pellucidum. (12)

Due to the limited available literature and research, there is currently no established treatment protocol for spinal GBM, and management strategies are generally based on those for intracranial glioblastoma. Current treatment options include subtotal resection, gross total resection or biopsy, followed by radiotherapy and chemotherapy. (16)

The benefits of gross total resection (GTR) are debated, with many studies indicating no significant survival advantage due to the tumor's infiltrative nature; in some cases, GTR has even led to worse outcomes. (16,18,19) For instance, in our study, the patient who underwent GTR was the youngest but had the shortest overall survival (9 months). Some studies suggest that the extent of resection is not a reliable prognostic factor for overall survival in spinal GBMs, [22, 20, 23] and extensive surgical manipulation may increase the risk of tumor cell seeding and dissemination. [8,9]

The extent of surgical resection does not appear to affect survival length; instead, patients with less tissue involvement tend to have a better prognosis, as noted by Jokovic et al [21]. Surgery and adjuvant therapies are often more effective for lesions that are smaller and at an earlier stage, with reduced risks of intraoperative dissemination and surgical complications.

The effectiveness and timing of chemotherapy and radiotherapy remain controversial. (24,9) Cheng et al. [25] found that postoperative radiotherapy combined with temozolomide improved prognosis, with a median overall survival of 15 months. Liu et al. [26] reported an overall survival of 20 months, but only one patient showed improvement in postoperative neurological status despite adjuvant treatments. Konar et al. [9] observed a median overall survival of 11 months in a literature review, with many patients reporting a poor quality of life. Early diagnosis and careful treatment may enhance overall survival and quality of life to some extent.

CONCLUSION

Primary spinal glioblastomas are rare and universally fatal, with frequent recurrence. These tumors are usually rapidly progressive, locally infiltrative, and may not be completely resectable, leading to poor outcomes despite aggressive treatment. Currently, there is no specific management protocol for spinal GBMs. The size of the tumor and preoperative neurological status seem to influence outcomes more than histopathology. Early diagnosis and treatment are associated with better outcomes and longer overall survival. Surgery remains the primary treatment, but the role of adjuvant therapy is not well-defined. More research and larger studies are needed to develop improved strategies for better outcomes.

INFORMED CONSENT

This study was approved by the Institutional Ethics committee of Mahatma Gandhi Medical College Jaipur 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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