

## Adjuvant Radiation Therapy and Temozolomide in Gliosarcoma: Is It Enough? Case Series of Seven Patients

### Abstract

**Objective:** We present our experience of gliosarcoma (GSM) in oncology tertiary care center over the last 5 years. **Materials and Methods:** We carried out a retrospective analysis of seven patients with GSM diagnosed between April 2008 and December 2012. Demographic data, clinicopathological data, treatment strategies employed, details of recurrence, and survival patterns were reviewed. **Results:** The median age at diagnosis was 54 years, ranging between 34 and 63 years with a female predominance (57.1% females). Headache and neurological deficit were the most common symptoms with parietal region being the most common site of lesion. Subtotal resection followed by concurrent chemoradiation therapy was delivered to six patients. The results following completion of planned schedule of concurrent chemoradiotherapy were quite disappointing with two patients having no evidence of disease, one patient was lost to follow-up, and other three had progressive disease. One patient with progressive disease subsequently received eight cycles of bevacizumab on a clinical trial protocol. Fifteen-month posttreatment, she had stable disease on follow-up. **Conclusions:** Our experience suggests that despite treatment, the diagnosis of GSM portends a poor prognosis and the use of bevacizumab could represent a treatment approach to improve outcome in these patients. Although the role of targeted therapy in GSM remains unclear because of paucity of experience, the treatment decision should be according to patient's performance status, ability, and willingness to receive additional treatment.

**Keywords:** *Bevacizumab, central nervous system neoplasms, chemoradiotherapy, gliosarcoma, headache, prognosis*

### Introduction

Gliosarcoma (GSM) is a rare, high-grade variant of glioblastoma multiforme (GBM) characterized by a biphasic pattern showing glial and mesenchymal components.<sup>[1]</sup> This neoplasm was first described by Stroebe in 1895.<sup>[2]</sup> Epidemiology and natural history of this tumor is not well defined. It usually affects individuals in 5<sup>th</sup>–6<sup>th</sup> decade of life with slight male preponderance.<sup>[3]</sup> Due to the lack of reported literature on the management of GSM, it is generally treated according to the prevailing guidelines for GBM. In patients with good performance status, optimal treatment for GSM includes maximal surgical decompression followed by postoperative chemoradiotherapy. In the light of current knowledge, it is suggested that GSM might be a distinct clinicopathological entity with certain unique features mainly its clinical propensity for extracranial metastasis, distinct radiological features, and possibly worse

prognosis as compared to GBM.<sup>[4]</sup> Even with the best of multimodality treatment, GSM has a poor prognosis and a propensity for distant metastasis with the usual site of involvement being lung followed by liver and bone.<sup>[5]</sup> The objective of this study is to report a series of GSM cases treated at a tertiary oncology care center.

### Materials and Methods

This study was approved by the Ethics Committee of the hospital. Medical records of all cancer patients treated in the Department of Radiation Oncology, Rajiv Gandhi Cancer Institute and Research Centre, New Delhi, from April 2008 to December 2012, were reviewed to identify the patients with histopathological diagnosis of GSM. From this data, we could retrieve seven cases of GSM. Age and demographic characteristics were noted. Clinicopathological data, treatment strategies employed, details of recurrence, and survival patterns were obtained from

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the patient case record forms. All patients underwent pretreatment evaluations including history, physical examination, preoperative computed tomography scans and/or magnetic resonance imaging of the brain, chest X-ray, ultrasound abdomen, and routine laboratory tests.

### Surgery

All patients underwent surgery in the form of craniotomy and excision of the tumor with curative intent. Unfortunately, only subtotal resection could be achieved in most of the patients.

### Radiotherapy

Patients were immobilized using thermoplastic cast and computed tomography simulation, and treatment planning was done according to the departmental protocol. All patients were treated on 6MV linear accelerator by three-dimensional conformal radiation therapy. Contouring of target volume was done as per the institutional protocol in two phases. In Phase I, gross tumor volume 1 (GTV1) represented T2-weighted postoperative abnormality on scan. Clinical target volume 1 (CTV1) included a margin of 2 cm around GTV1. A margin of 5 mm around CTV1 was used to account for setup error (defined as planning target volume 1 [PTV1]). In Phase II, GTV2 represented contrast-enhanced T1 postoperative abnormality. A margin of 2 cm and 0.3–0.5 cm around GTV2 accounted for CTV2 and PTV2, respectively. Adjuvant radiotherapy (RT) was delivered on outpatient basis at 2 Gy/F, given 5 days/week, over a period of 6 weeks. Dose of 46 Gy/23 F was delivered to PTV1 in Phase I followed by 14 Gy/7 F to PTV2 in Phase II.

### Chemotherapy

Concurrent chemotherapy comprised temozolomide (TMZ) (75 mg/m<sup>2</sup>/day) with antiemetic prophylaxis starting from the day of RT for 42 consecutive days. The blood counts were monitored weekly for hematological toxicity in terms of leukopenia and/or thrombocytopenia. After a break of 4 weeks, patients were offered six cycles of adjuvant TMZ, beginning with a dose of 150 mg/m<sup>2</sup>/day as per the 5-day schedule every 28 days. Dose was further escalated to 200 mg/m<sup>2</sup>/day from next cycle if the patient tolerated the first adjuvant cycle.

### Follow-up

All patients were followed up in the radiation oncology outpatient department monthly for 3 months, 2 monthly for 6 months, and 3 monthly thereafter. Each follow-up visit included complete physical and neurological examination, along with routine blood count. The patient was evaluated with magnetic resonance imaging brain after 3 months following completion of adjuvant TMZ or in case of symptomatic deterioration.

### Response assessment

Demographic data and clinicopathological variables were evaluated. Overall survival (OS) was calculated from

the date of diagnosis of GSM till date of death or last follow-up. Survival outcomes of GSM were compared with the historical data. All data were analyzed using SSS Statistics 17.0; SPSS Inc., Chicago, IL, USA.

### Results

Seven patients with histopathological diagnosis of GSM were retrospectively analyzed at Rajiv Gandhi Cancer Institute and Research Centre, New Delhi. All patients were adults and the mean age at diagnosis ranged between 34 and 63 years (median age = 54). Male to female ratio was 3:4. Pretreatment Karnofsky performance status (KPS) was 70 in 28.57%, 60 in 14.28%, 50 in 28.57%, and 40 in 28.57% patients. Most common symptoms at the time of presentation were motor neurological deficits (42.85%) and those due to raised intracranial tension (42.85%). Other less common symptoms included seizures, urinary incontinence, and forgetfulness in 1 (14.28%) patient each. Median duration of presenting symptoms was 75 days (range, 15–120 days). The most common location of GSM was parietal region (57.1%) followed by frontal region (28.6%) and temporal region (14.3%). All GSM patients showed two characteristic patterns on preoperative magnetic resonance imaging: (1) peripheral tumor with dural thickening (71.42%) and (2) central lesion infiltrating the ventricles (28.57%). Satellite lesion was noticed in two patients.

All patients underwent craniotomy with attempt to achieve gross total surgical resection. Unfortunately, total resection could be achieved in only two patients; remaining five patients underwent subtotal resection. There were no peri- or post-operative complications seen in any patient. All patients underwent single operative procedure only. Mean interval between surgical procedure and adjuvant RT was 24 days. Six GSM patients completed the planned course of 60 Gy in 30 F irradiation along with concurrent TMZ without any interruption of treatment. One patient expired after receiving 21 F due to progression of the disease. Only two patients completed six cycles of adjuvant chemotherapy with TMZ. All the remaining patients defaulted for the planned treatment. Thus, current standard of care, that is, Stupp *et al.*'s protocol,<sup>[6]</sup> was followed for only two GSM patients.

Median OS for all GSM patients was 6.3 months and 1-year OS was 28.6% [Figure 1]. Only one patient with progressive disease subsequently received targeted therapy in the form of bevacizumab after TMZ on a clinical trial protocol. This patient received eight cycles of bevacizumab with stable disease at the last follow-up visit (15 months) [Figure 2].

### Discussion

GSM is a rare tumor constituting approximately 2% of all glioblastoma and accounts for 0.59%–0.76% of all

adult brain tumors. It typically affects older men, with onset between the fourth and sixth decades of life and a male to female ratio of 1.8:1.<sup>[7]</sup> Among the seven patients, we found 57.15% females to be affected by this disease. Majority of our patients (57.1%) presented with parietal lobe lesion. GSM is almost never found infratentorially and the majority of the reports describe its temporal lobe predilection.<sup>[8-10]</sup> In our series, the most common symptoms at presentation were motor neurological deficits as well as those due to raised intracranial tension (42.85%) with a median duration of 75 days of these symptoms. Damodaran *et al.*<sup>[11]</sup> conducted a clinical study on patterns of care and outcomes for a series of Australian patients diagnosed with GSM. They reported pretreatment KPS of 100 in 21% of patients, 70–90 in 53%, 50–60 in 11%, and for the remaining (15%), score was not recorded. Contradictory to this, we found KPS  $\leq 60$  in 71.42% and 70 in 28.57% patients. This finding indicated that majority of GSM patients presented with a poor performance status.

Histopathological characteristics showed a mixture of glial and sarcomatoid components with areas of microvascular proliferation and necrosis. Immunohistochemically, gliomatous component was positive for glial fibrillary acidic protein [Figure 2a-d]. Origin of GSM has been a source of controversy. Historically, the sarcomatous element of GSM was thought to be the result of cancerous alteration of hyperplastic blood vessels as found in high-grade gliomas. However, recent theory points to monoclonal origin of both elements of GSM, i.e., mesenchymal differentiation of glioma gives rise to sarcomatoid element.<sup>[4,12]</sup>

GSM has been reported to be resistant to the currently available treatment options due to the presence of glioma stem cells. Hassiotou *et al.*<sup>[13]</sup> reported that GSM to be a different and even more aggressive variant of GBM due to the presence of different lineages in GSM responsible for its greater heterogeneity. This highlights that the treatment plan for these patients needs to be individualized keeping in mind the performance status of the patient and cost-effectiveness of the treatment. To date, no published guidelines exist for the management of GSM patients. A recent retrospective single-institutional analysis of 27 patients with primary GSM treated with concurrent and adjuvant TMZ showed an impressive median survival of 21.21 months with acceptable toxicity. The authors suggested TMZ to be included in the “standard of care” for this tumor.<sup>[14]</sup> Contrary to this, no difference in the length of survival was noted between patients with GSM receiving RT with TMZ compared with those who did not.<sup>[15]</sup> However, this study had small sample size and lack of statistical power for adequate analysis of the potential therapeutic benefit of RT with TMZ. Tumor resection, postoperative radiation therapy, and chemotherapy with nitrosoureas, misonidazole, dacarbazine, mithramycin, amethopterin, thalidomide, TMZ, irinotecan, vincristine, cisplatin, or doxorubicin are among the available treatment options for

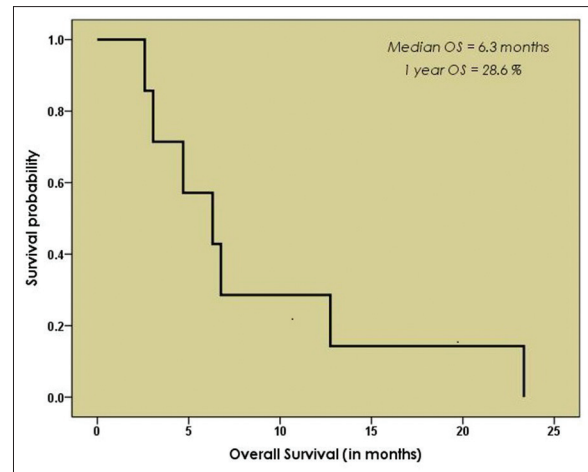


Figure 1: Overall survival analysis for all gliosarcoma patients

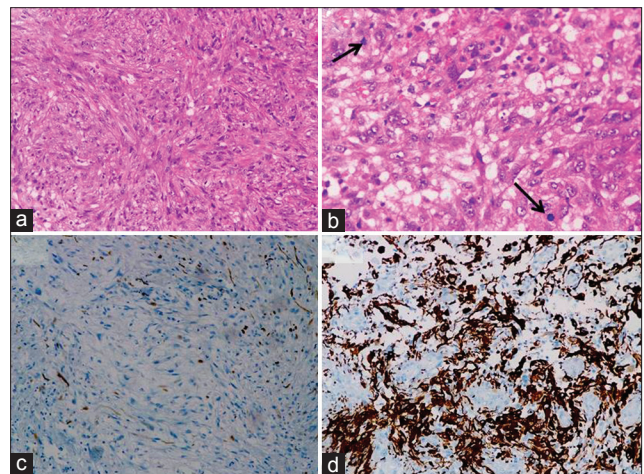


Figure 2: (a) Sarcomatous pattern with neoplastic spindle cells in fascicles (H and E;  $\times 200$ ), (b) classical gliomatous areas with brisk mitosis (arrow) (H and E;  $\times 400$ ), (c) poor glial fibrillary acidic protein expression in sarcomatous area (DAB;  $\times 200$ ), (d) gliomatous component showing a significant glial fibrillary acidic protein staining in tumor cells (DAB;  $\times 200$ )

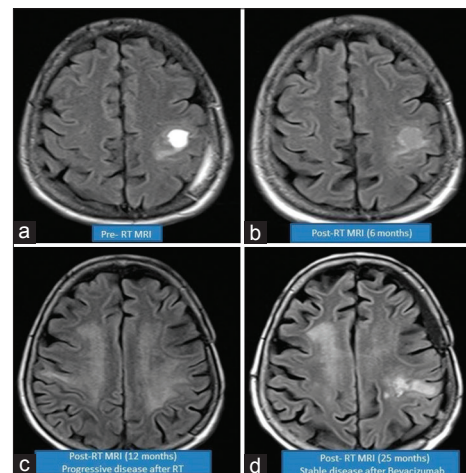


Figure 3: Radiological response of adjuvant bevacizumab in a patient with GSM

these patients.<sup>[5,8,16]</sup> We have treated our GSM patients with multimodality treatment in the form of surgical resection,

mostly subtotal resection was possible followed by adjuvant chemoradiation therapy with TMZ. Five patients could complete scheduled doses of adjuvant TMZ. This treatment is in accordance with the literature suggesting the use of TMZ at the same time as RT as a first-line treatment at doses of 75 mg/m<sup>2</sup>/day 1 h before RT and at weekends and after the RT treatment is concluded as an adjuvant treatment in doses of 150 mg/m<sup>2</sup> for five cycles. With this treatment protocol, a slight increase in survival (2-year survival of 26.5% with RT-TMZ combination as compared with 10.4% with RT alone. Median survival of 12.1 months and 14.6 months, respectively) has been reported in the literature.<sup>[17]</sup> Recent molecular studies have shown that patients with primary GSM have promoter methylation of O6-methylguanine deoxyribonucleic acid methyltransferase in 30%–50% of the patients, predicting a better response from TMZ.<sup>[18,19]</sup> However, the prognosis of GSM remains poor over the several years despite advances in multimodality treatment. Our results of the treatment showed median OS of 6.3 months from the date of diagnosis and it appears comparable to results obtained in other similar case series<sup>[4,8,20]</sup> who have reported a mean survival for GSM patients as 13 months (6.9–19.4 months).

In the 2007 World Health Organization classification of central nervous system tumors, it considered GSM as a subtype of glioblastoma. This conclusion was supported by finding identical genetic alterations in both tumor elements.<sup>[21]</sup> In addition, gliomas are highly vascular tumors, rich in vascular endothelial growth factor (VEGF) promoting new blood vessel formation. Bevacizumab is a humanized anti-VEGF monoclonal antibody that inhibits VEGF and is effective for recurrent glioblastoma, extending progression-free survival and improved quality of life in various clinical trials.<sup>[22]</sup> Bevacizumab is approved for use in recurrent GBM patients by FDA based on the clinical benefits observed in two recent Phase II trials.<sup>[23,24]</sup> Since there is no established treatment for disease progression after the initial treatment with adjuvant RT and TMZ, we planned to treat one GSM patient with eight cycles of bevacizumab on disease progression and this patient had regression of tumor on imaging with survival of 15 months [Figure 3a-d]. Although at present, there is very little data available regarding the response of GSM to targeted therapies. A Phase II trial is ongoing estimating OS in elderly subjects treated with bevacizumab and TMZ for newly diagnosed GBM or GSM.<sup>[25]</sup> A survival time of 15 months was found to be definitely longer than for patients without any treatment on disease progression.

However, keeping in mind that our patient showed a good response to bevacizumab, we propose that clinicians should keep targeted therapy as a potential viable option for GSM patients and its inclusion in the treatment protocol may possibly enhance the outcome of this grave disease. However, it remains difficult to select patients who would respond to this treatment or whether to provide best

supportive care to these patients on disease progression. The critical role of targeted therapy in GSM needs to be determined in the setting of larger case series in the near future.

After thorough search of the literature, we found case report of one patient with three different brain tumors: astrocytoma, glioblastoma, and GSM. Genetic analysis underlying the three different histological groups reported that they were derived from a common origin but each with unique genetic alterations. GBM had PDGFRA amplification, whereas GSM had MYC amplification. This patient died 10 months following diagnosis. The authors concluded that genetic heterogeneity is mainly responsible for the treatment failure, changing our focus on determining molecular markers that determine response in individual patients.<sup>[26]</sup>

The present study had certain notable limitations. First, we had less number of patients to reach at a firm conclusion regarding the best treatment option. Second, IHC staining tests should have been done on the biopsy specimen to confirm the diagnosis as primary or secondary GSM (such as vimentin and cytokeratin).

## Conclusion

Our work serves to highlight that GSM is a unique entity with grim prognosis. The treatment of these patients is particularly challenging and should be individualized depending on the fitness and tolerability of the patient. It is thought provoking that, despite aggressive multimodality treatment, the survival of this disease remains poor suggesting that the decision needs to be weighed regarding switching to newer therapeutic approaches after testing these tumors for specific mutations providing a better insight into a specific patient subpopulation that might respond better with an improvement in prognosis or moving toward best supportive care to provide a better quality of life. We believe that our data laid a foundation regarding the role of targeted therapy in the management of this disease and future efforts should be directed toward establishing the same. However, evaluation of our data with larger series of patients is strongly recommended to derive a firm conclusion.

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## Conflicts of interest

There are no conflicts of interest.

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