Clinical Study

Clinical management and survival outcomes of gliosarcomas in the era of multimodality therapy

Omprakash Damodaran [a,*], Jolandi van Heerden [b], Anna K. Nowak [c,d], Michael Bynevelt [b], Kerrie Mcdonald [e], Julie Marsh [d], Gabriel Lee [d,f]

[a] Liverpool Hospital, Elizabeth Street, Liverpool, NSW 2170, Australia
[b] Neurological Intervention and Imaging Service (WA), Sir Charles Gairdner Hospital, Perth, WA, Australia
[c] Department of Medical Oncology, Sir Charles Gairdner Hospital, Perth, WA, Australia
[d] University of Western Australia, Perth, WA, Australia
[e] Prince of Wales Clinical School, University of New South Wales, Randwick, NSW, Australia
[f] Department of Neurosurgery, Sir Charles Gairdner Hospital, Perth, WA, Australia

ARTICLE INFO

ABSTRACT

Gliosarcoma (GSM) is a rare primary malignant brain tumour accounting for less than 0.5% of all intracranial tumours. It has a biphasic histological composition, demonstrating both gliomatous and sarcomatous elements. In clinical practice GSM are generally managed similarly to glioblastoma multiforme (GBM). However, unique features including its clinical propensity for extra-cranial metastasis, distinct radiological features and possible worse prognosis than GBM suggest that GSM may be a distinct clinico-pathological entity. Hence we reviewed patterns of care and outcomes for a series of Australian patients diagnosed with GSM in the era of combined chemo-radiotherapy. Patients were identified by searching the Australian Genomics and Clinical Outcomes of Glioma (AGOG) database and the Western Australian Interhospital Neurosurgical database. Nineteen patients with GSM were identified. Of these, 15 patients were diagnosed with primary GSM and four patients developed secondary GSM after radiation therapy for primary GBM. For comparative purposes, 408 primary GBM patients were identified from the AGOG database during the same study period. The overall median survival for all primary GSM patients was 9.7 months. In comparison the overall median survival for GBM patients recruited to the AGOG database over the same period was 12.2 months. The median survival for secondary GSM patients from the time of diagnosis was 5 months. Primary and secondary GSM pose a great clinical challenge due to their rarity. Our study adds further evidence to support GSM as a unique clinical entity with a likely worse prognosis than GBM.

1. Introduction

Gliosarcoma (GSM) is a rare primary malignant brain tumour accounting for less than 0.5% of all intracranial tumours [1]. It has a biphasic histological composition, demonstrating both gliomatous and sarcomatous elements [2]. The glial component meets the histological criteria for World Health Organization grade IV astrocytoma (glioblastoma multiforme; GBM) [2]. The mesenchymal component usually resembles fibrosarcoma but may show varied morphologies resembling osteosarcoma, chondrosarcoma, angiosarcoma and/or rhabdomyosarcoma [2,3]. *De novo* GSM are termed primary gliosarcoma, whereas secondary GSM are lesions that develop in previously resected and irradiated GBM. Given the distinct histopathological features of the two components of GSM, there is an intuitive expectation that these lesions may demonstrate differential responsiveness to treatment. Yet in clinical practice GSM are generally managed in accordance with the prevailing guidelines for GBM [4]. In patients with good functional status, optimal treatment for GBM now includes maximal surgical resection followed by radiotherapy and chemotherapy. This multi-modality management approach has been extrapolated to become the standard of care for GSM [3]. However, unique features of GSM including its clinical propensity to undergo extra-cranial metastasis, distinct radiological features and possible worse prognosis in comparison to GBM suggest that this may be a distinct clinico-pathological entity [4]. Hence we reviewed patterns of care and outcomes for a series of Australian patients diagnosed with GSM in the era of combined chemo-radiotherapy.

* Corresponding author. Tel.: +61 2 9828 3000; fax: +61 2 9649 1431.
E-mail address: domprakash@hotmail.com (O. Damodaran).

2. Methods

Patients were identified by searching the Australian Genomics and Clinical Outcomes of Glioma (AGOG) database and the Western Australian Interhospital Neurosurgical database.

The AGOG database is a prospective registry of consecutive patients diagnosed with a new glioma recruited from six major neurosurgical sites in two Australian states, New South Wales and Western Australia. The database collects clinical information on pathology, surgery, chemotherapy, radiotherapy, and survival outcomes, together with matching biological specimens and radiology. The database has Institutional Human Research Ethics Committee approval and participants provide written informed consent for inclusion. The Western Australian Interhospital Neurosurgical database prospectively collects information on admissions to the service.

The databases were searched for GSM patients diagnosed between 2005 and July 2012. Patients from each database were cross-checked to prevent duplicate inclusion. Clinical, surgical and radiographic data were also confirmed through retrospective chart review. The extent of tumour resection was established using operative notes and postoperative imaging (CT scan or MRI) and quantified as gross total or subtotal resection. Where there was inadequate clinical information to confirm the extent of resection accurately, it was documented as "unable to quantify". Findings on preoperative images were based both on the radiology report and also through an independent review of images by two neuroradiologists (J.V.H. and M.B.). Survival was calculated from the date of diagnosis of GSM to the date of death. Statistical analysis was conducted using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA).

3. Results

3.1. Clinical characteristics

At the time of data analysis, 19 patients with GSM were identified from the two databases. Of these, 15 patients were diagnosed with primary GSM and four patients developed secondary GSM after radiation therapy for primary GBM. For comparative purposes, 408 primary GBM patients were identified from the AGOG database during the same study period. Of the 19 patients with GSM, the median age was 58.6 years (range 34–86) and 58% were male. The median age of patients with GBM was 58.9 years (range 21–85) with a male predominance (65% male). Neither of these characteristics differed significantly between groups. The pretreatment Karnofsky performance score for GSM patients was 100 in 21% of patients, 70–90 in 53%, 50–60 in 11%, and a score was not recorded in 15%. GSM patients all presented with signs and symptoms associated with raised intracranial pressure and seizure was not the primary presentation in any patient.

3.2. Radiological characteristics

Preoperative MRI studies were reviewed in all primary and secondary GSM patients. The majority of primary GSM were situated in the temporal lobe (47%). The remaining lesions were located in the frontal (27%) and parietal (13%) lobes, and parieto-temporal region (13%). Half of the secondary GSM (50%) were found in the frontal lobe and the remainder in the parieto-temporal region. None of the primary or secondary GSM in our series involved the occipital region or posterior fossa. The majority of primary GSM (67%) and all secondary GSM were peripherally situated.

In 47% of primary GSM, the tumours demonstrated low signal on T2-weighted images (T2WI) with corresponding high signal on diffusion weighted images (DWI) and low signal on apparent diffusion coefficient (ADC) maps. The rest of the primary GSM as well as 75% of the secondary GSM demonstrated mixed signal on T2WI, DWI and ADC maps. The primary and secondary GSM demonstrated irregular, nodular rim enhancement, with heterogeneous central tumour enhancement present in 13% of primary GSM and 50% of secondary GSM.

GSM demonstrated two predominant patterns on MRI: (1) a peripheral location involving cortex associated with dural thickening (Fig. 1); and (2) a central location with transependymal infiltration into the ventricles. Dural thickening and enhancement were noted in all the peripherally situated tumours. The majority of primary GSM were peripherally situated (67%) and all secondary GSM demonstrated a peripheral location. Additional smaller rim-enhancing satellite lesions were noted in 60% of the centrally located primary GSM, in 50% of the peripherally situated primary GSM and in 25% of the secondary GSM.

3.3. Surgical treatment

All 19 patients underwent a craniotomy and macroscopic resection of the tumour rather than a limited diagnostic biopsy. In 63% of patients macroscopic gross total resection was achieved, 21% achieved subtotal resection and in 16% the extent of resection was not specified. There were no operative mortalities or major postoperative complications. All primary GSM patients underwent only one surgical procedure.

3.4. Post-surgical treatment and survival

3.4.1. Primary GSM

Thirteen out of 15 (87%) patients with primary GSM underwent three-dimensional conformal radiotherapy (3D-CRT). Two patients did not receive radiotherapy or chemotherapy due to rapid clinical deterioration and death. Eleven out of 12 patients (92%) received 60 Gy in 30 fractions of radiotherapy. One elderly patient had a planned two-phase radiation treatment schedule which consisted of 35 Gy 3D-CRT in 15 fractions and 30 Gy 3D-CRT in 10 fractions. All primary gliosarcoma patients completed their planned course of irradiation.

Twelve patients (80%) were treated with radiotherapy (60 Gy in 30 fractions) and concurrent and adjuvant temozolomide based on the protocol described by Stupp et al. for GBM [5], with two also
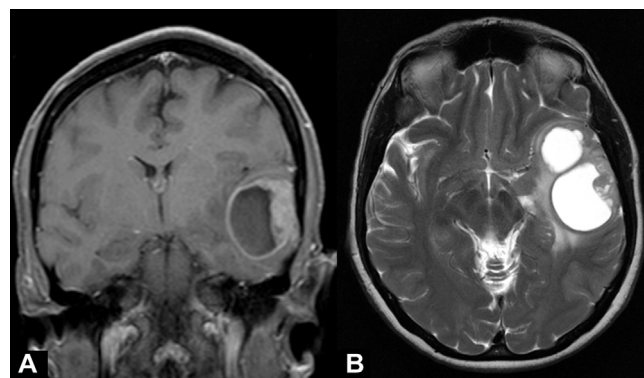

Fig. 1. (A) Coronal T1-weighted MRI with gadolinium enhancement demonstrating the more peripheral distribution type of primary gliosarcoma with cortical and subcortical involvement of the left temporal lobe. The lesion has a dural base with associated dural thickening and enhancement extending inferiorly from the lateral margin of the lesion. The lesion demonstrates irregular rim enhancement but remains relatively well demarcated. (B) Axial T2-weighted MRI of the brain showing lesion involvement of the periphery of the left temporal lobe with associated peri-lesional T2-weighted high signal and mass effect.

receiving pegylated liposomal doxorubicin hydrochloride (CAELYX; Janssen-Cilag, North Ryde, NSW, Australia) during the adjuvant phase as part of a clinical trial. The elderly patient (7%) who received 3D-CRT in two phases received sequential temozolomide following completion of radiotherapy. The two patients (13%) who did not receive radiotherapy also did not receive chemotherapy. Two patients subsequently received carboplatin and bevacizumab as combined therapy after temozolomide on a clinical trial protocol. Other agents used at the time of recurrence included a combination of temozolomide and procarbazine (n = 2) as well as carboplatin monotherapy (n = 2).

Survival information from the time of diagnosis was available for all patients and five patients were confirmed to be alive at the time of data analysis. The overall median survival for all primary GSM patients was 9.7 months. In comparison the overall median survival for GBM patients recruited to the AGOG database over the same period was 12.2 months (hazard ratio 1.54; 95% confidence interval 0.82–2.91; p = 0.18 after adjustment for age at diagnosis) (Fig. 2).

3.4.2. Secondary GSM

All four patients with secondary GSM received 3D-CRT, with 60 Gy in 30 fractions in combination with concurrent and adjuvant temozolomide after their initial diagnosis of GBM [5], with one patient also treated with adjuvant CAELYX on a clinical trial. One patient received further radiotherapy to scalp metastases (18 Gy in 1 fraction, 3D-CRT) after transformation to secondary GSM. This was the only patient in the series to develop metastatic disease. Two out of the four patients underwent three or more surgical procedures at the time of symptomatic recurrence. These patients also received agents such as procarbazine, bevacizumab and carbo-
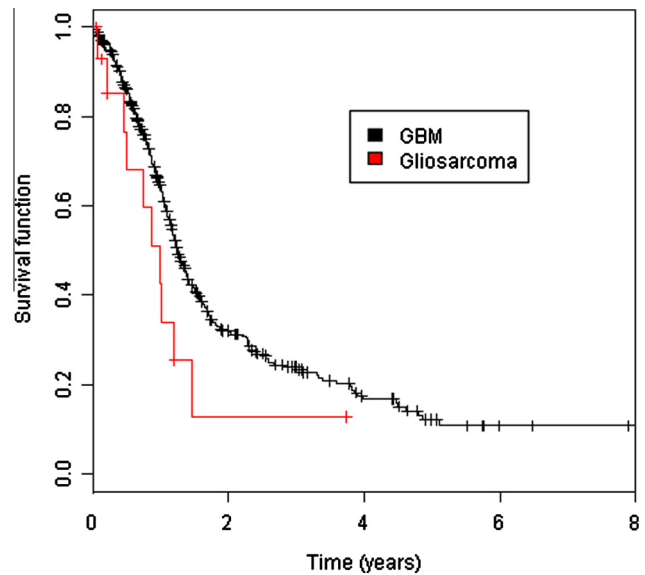
Fig. 3. Kaplan–Meier survival curve showing comparison of overall survival of glioblastoma (GBM) *versus* primary gliosarcoma.

platin after their transformation to secondary GSM. The median elapsed time from the initial diagnosis of GBM to subsequent diagnosis of secondary GSM from a further surgical procedure was 18 months. The overall median survival in these four patients from the initial diagnosis of GBM was 21 months, with the median survival from the time of diagnosis of secondary GSM being 5 months (range 4–23 months) (Fig. 3).

4. Discussion

This Australian series describes the clinical and imaging characteristics, contemporary patterns of care and outcomes for patients with GSM identified through two large unselected databases. Patterns of care demonstrate that in current clinical practice, fit patients with GSM are routinely treated with maximal safe surgical resection followed by combined chemo-radiotherapy (3D-CRT to 60 Gy in conjunction with concurrent and adjuvant temozolomide).

The pathogenesis of primary and secondary GSM has been a source of controversy. It was thought to be a "collision tumour", with the sarcomatous component originating from neoplastic transformation of hyperplastic blood vessels found in high grade gliomas [2,6]. An alternative and more recent theory is the monoclonal origin of both components of GSM, with the sarcomatous element arising via aberrant mesenchymal differentiation of malignant glioma [2,6]. The monoclonal origin is further supported by similar genetic alterations, including p53 mutations, p16 deletions and phosphatase and tensin homolog (PTEN) mutations found in both the gliomatous and the sarcomatous components [7].

GSM are clinically indistinguishable from GBM [8]. The reported incidence varies between 1.8–8% of GBM patients. The peak incidence is seen in the sixth and seventh decades of life, similar to the median age of 58.6 years seen in our series [2]. Unique features of GSM documented in the literature include the potential to appear similar to meningioma at surgery, temporal lobe predilection, extra-cranial metastasis and infrequency of epidermal growth factor receptor (EGFR) mutations. Most studies report a high incidence of primary GSM either in the temporal or frontal lobe [1,9]. Concordant with the literature, our series also

Fig. 2. Axial T1-weighted MRI with gadolinium enhancement showing a more central distribution of primary gliosarcoma with transependymal, intraventricular extent. Irregular enhancement of the lesion margin is again demonstrated.

showed a temporal lobe predilection, followed by frontal lobe tumour involvement. We also noted that 67% of primary GSM as well as all secondary GSM were located peripherally with associated dural involvement. Although these imaging characteristics do not currently have therapeutic significance, they have also been noted in other series [1]. Most GSM are described as well-demarcated, irregular lesions and this was also noted in our series [1]. True multifocal GSM are rare with only a few reported cases [1]. Although we noted the occurrence of satellite lesions associated with both primary and secondary GSM, there were no true multifocal GSM.

The median reported survival for untreated patients with primary GSM is 4 months [9], with radiation therapy delivering an improvement in median survival from 6.25 months to 10.6 months in one study [10]. Kozak et al. in his retrospective study based on the Surveillance, Epidemiology and End Results (SEER) database identified age, extent of resection and adjuvant radiotherapy as factors affecting overall survival [9]. He also concluded that GSM had a slightly worse prognosis than GBM [9]. This finding of worse overall survival for GSM patients compared to GBM has also been reported in other retrospective studies without reaching statistical significance [2,3]. In our series GSM patients had an overall worse survival compared to the GBM group (9.7 *versus* 12.2 months). However, the difference in survival failed to reach statistical significance ($p = 0.18$), with relatively small numbers of GSM patients making the series underpowered to show a significant survival difference.

Our study highlights that currently GSM are managed similarly to GBM in Australia, with maximal safe surgical resection followed by chemo-radiotherapy as described by the Stupp protocol [11]. A recent single institution retrospective series of GSM patients reported improved survival with the Stupp protocol [13]. This study by Walker et al. reported 17 patients treated with radiotherapy as well as concurrent and adjuvant temozolomide [13]. These 17 patients had a 24 month overall survival of 20% compared to 10.2% among patients who were not treated with this regimen; however, this survival difference did not reach statistical significance [13]. In contrast, Han et al. reported 10 GSM patients treated with the Stupp protocol with worse median survival compared to 10 GSM patients who were not treated with this regimen (0.4 months *versus* 13.9 months) [11]. In our study 80% of the patients were treated with the Stupp protocol, hence a comparison is not possible.

Secondary GSM is also uncommon, with the largest series to our knowledge published in 2010 with only 30 patients [4]. This series reported a median survival of 4.4 months from the diagnosis of secondary GSM [4]. In our study the median overall survival for secondary GSM from the initial diagnosis of GBM was 21 months and the median survival from the diagnosis of secondary GSM was 5 months. Han et al. postulated that the recent increase in the number of secondary GSM diagnosed could be due to more aggressive GBM treatment approaches [4]. This is intuitive as a diagnosis of secondary GSM cannot be made without subsequent surgery; however, the reported increased incidence of secondary GSM may also be related to increased diagnostic awareness of this condition [4]. The sarcomatous transformation seen in GBM could be associated with worse prognosis and alkylating chemotherapeutic agents may also be less effective when sarcomatous elements are present [4,12]. Future studies examining O(6)-methylguanine-DNA methyltransferase (MGMT) status in primary and secondary GSM might be helpful in clarifying the role of temozolomide in treating this unique clinical entity [4,12].

The main limitation of the current study is its retrospective nature; however, large prospective studies are difficult to design given the rarity of both primary and secondary GSM [11]. The study cohort may also have a bias towards collecting younger patients or those with a better performance status, as written informed consent was a requirement for recruitment to AGOG. Despite these limitations, the multi-centre approach has provided a means of collating a substantial number of patients with this uncommon entity.

5. Conclusion

Primary and secondary GSM pose a great clinical challenge due to their rarity [2,3]. Despite aggressive surgical resection and modern multi-modality therapy, the prognosis remains poor. Although they are clinically indistinguishable from GBM, imaging features such as a predilection for the temporal and frontal lobes as well as a peripheral tumour location with dural involvement should alert the clinician to consider GSM as part of their differential diagnosis. Currently GSM are treated similar to GBM with maximal surgical resection followed by chemo-radiotherapy and adjuvant temozolomide. Our study adds further evidence to support GSM as a unique clinical entity with a likely worse prognosis than GBM. Further rigorous research into the clinical, genomic and molecular characteristics of GSM is required to better understand this malignant brain tumour.

Conflicts of interest/disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

Acknowledgements

References

[1] Zhang BY, Chen H, Geng DY, et al. Computed tomography and magnetic resonance features of GSM: a study of 54 cases. J Comput Assist Tomogr 2011;35:667–73.
[2] Biswas A, Kumar N, Kumar P, et al. Primary GSM-clinical experience from a regional cancer centre in north India. Br J Neurosurg 2011;25:723–9.
[3] Kumar P, Singh S, Krishnani N, et al. GSM: an audit from a single institution in India of 24 post-irradiated cases over 15 years. J Cancer Res Ther 2008;4:164–8.
[4] Han SJ, Yang I, Otero JJ, et al. Secondary GSM after diagnosis of glioblastoma: clinical experience with 30 consecutive patients. J Neurosurg 2010;112:990–6.
[5] Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–96.
[6] Han SJ, Yang I, Tihan T, et al. Primary GSM: Key clinical and pathologic distinctions from glioblastoma with implications as a unique oncologic entity. J Neurooncol 2010;96:313–20.
[7] Lin JW, Wu YT, Chang IW. The prognostic impact of O6-methylguanine DNA methyltransferase and epidermal growth factor receptor expressions on primary GSM: a clinicopathologic and immunohistochemical study of seven cases at a single institution. Indian J Pathol Microbiol 2011;54:683–7.
[8] Chen L, Xiao H, Xu L, et al. A case study of a patient with GSM with an extended survival and spinal cord metastases. Cell Biochem Biophys 2012;62:391–5.
[9] Kozak KR, Mahadevan A, Moody JS. Adult GSM: epidemiology, natural history, and factors associated with outcome. Neuro Oncol 2009;11:183–91.
[10] Perry JR, Ang LC, Bilbao JM, et al. Clinicopathologic features of primary and postirradiation cerebral GSM. Cancer 1995;75:2910–8.
[11] Han SJ, Yang I, Ahn BJ, et al. Clinical characteristics and outcomes for a modern series of primary GSM patients. Cancer 2010;116:1358–66.
[12] Han SJ, Yang I, Tihan T, et al. Secondary gliosarcoma: A review of clinical features and pathological diagnosis. J Neurosurg 2010;112:26–32.
[13] Walker GV, Gilbert MR, Prabhu SS, et al. Temozolamide use in adult patients with gliosarcoma: an evolving clinical practice. J Neurooncol 2013;112:83–9.