Cancer Association of South Africa (CANSA)

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Fact Sheet on Gliosarcoma

Introduction

Cancerous (malignant) tumours of connective tissues are called 'sarcomas'. Sarcoma arises in the connective tissue of the body. Normal connective tissue includes, fat, blood vessels, nerves, bones, muscles, deep skin tissues, and cartilage.

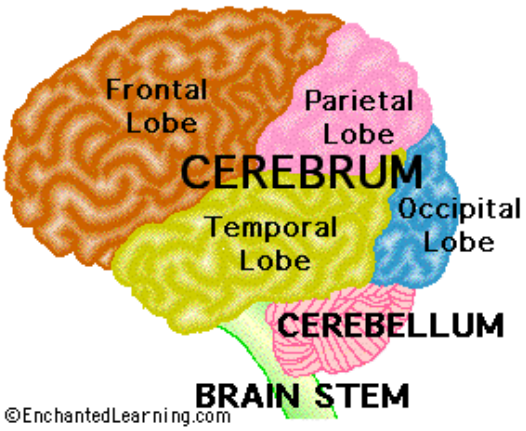
[Picture Credit: Gliosarcoma]

Sarcomas are divided into two main groups, bone sarcomas and soft tissue sarcomas. They are further sub-classified based on the type of presumed cell of origin found in the tumour. They all share certain microscopic characteristics and have similar symptoms.

Sarcomas can develop in children and adults. For children under 20 approximately 15 percent of cancer diagnoses are sarcomas.

Gliosarcoma

Gliosarcoma is a rare type of glioma, a cancer of the brain that comes from glial, or supportive, brain cells, as opposed to the neural brain cells. Glial cells, sometimes called neuroglia or simply glia (Greek γλία and γλοία 'glue'), are non-neuronal cells that maintain homeostasis, form myelin (a mixture of proteins and phospholipids forming a whitish insulating sheath around many nerve fibres, which increases the speed at which impulses are conducted), and provide support and protection for neurons in the central and peripheral nervous systems.



[Picture Credit: Parts of the Human Brain]

Gliosarcoma is a malignant cancer found mostly in the temporal lobe of the brain, and is defined as a glioblastoma consisting of gliomatous and sarcomatous components. It is estimated that

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approximately 2% of all glioblastomas are gliosarcomas. Although most gliomas rarely show metastases outside the cerebrum, gliosarcomas have a propensity to do so, most commonly spreading through the blood to the lungs, and also to the liver and lymph nodes.

Gliosarcomas have an epidemiology (study and analysis of the patterns, causes, and effects of health and disease conditions) similar to that of glioblastomas, with the average age of onset being 54 years, and males being affected twice as often as females.

Hashmi, F.A., Salim, A., Shamim, M.S. & Bari, M.E. 2018.
"Gliosarcoma is a highly aggressive primary brain tumour. It is a relatively rare tumour and comprises of two histological components, glial and sarcomatous. Gliosarcomas carry a poorer prognosis than that of Glioblastoma Multiforme (GBM)."

Wang, L., Sun, J., Li, Z., Chen, L., Fu, Y., Zhao, L., Liu, L., Wei, Y., Teng, L. & Lu D. 2017.
"Gliosarcoma, which is regarded as a variant of glioblastoma, is a rare malignant neoplasm of the central nervous system. Both its sarcomatous component and glial component are reported to share significant clinical and genetic similarities. However, gliosarcomas are considered to be characterised by a lack of the *BRAF* V600E mutation. Here, we report two cases of gliosarcoma harbouring the *BRAF* V600E mutation, of which one case appears to have arisen de novo, while the other likely arose from ganglioglioma. Interestingly, the *BRAF* V600E mutation was detected only in the glial component in the first case, but was present in both the glial and the sarcomatous components in the recurrent gliosarcoma. Furthermore, the different mutation state of *BRAF* V600E in our two cases suggests that the malignant transformation of gliosarcoma might have different underlying genetic alterations and mechanisms in de novo versus recurrent gliosarcoma."

Incidence of Gliosarcoma in South Africa
The National Cancer Registry (2016) does not provide information regarding the incidence of Gliosarcoma in South Africa.

The Cause of Gliosarcoma
Gliosarcoma seems to be a hereditary disorder. The genetic structure of sufferers is often believed to be mainly responsible for this clinical condition. Missing or mutated genes are suggested as leading to this abnormality in brain cells. The abnormal cells eventually form a tumour because of uncontrolled cell multiplication. Genetic structure is often the cause of the clinical condition. It is usually caused by mutated or missing genes that result in abnormal cells. These abnormal cells eventually will form a tumour when they multiply. It is usually hereditary.

Signs and Symptoms of Gliosarcoma
The most common signs include the following:

- Recurring headaches
- Vomiting

- Unsteadiness
- Vision loss
- Cognitive problems
- Seizures
- Personality changes

Frandsen, S., Broholm, H., Larsen, V.A., Grunnet, K., Møller, S., Poulsen, H.S. & Michaelsen, S.R. 2019.

Background: Gliosarcoma (GS) is a rare histopathologic variant of glioblastoma (GBM) characterized by a biphasic growth pattern consisting of both glial and sarcomatous components. Reports regarding its relative prognosis compared to conventional GBM are conflicting and although GS is treated as conventional GBM, supporting evidence is lacking. The aim of this study was to characterize demographic trends, clinical outcomes and prognostic variables of GS patients receiving standardized therapy and compare these to conventional GBM.

Methods: Six hundred and eighty GBM patients, treated with maximal safe resection followed by radiotherapy with concomitant and adjuvant temozolomide at a single institution, were retrospectively reevaluated by reviewing histopathological records and tumor tissue for identification of GS patients. Clinico-pathological- and tumor growth characteristics were obtained via assessment of medical records and imaging analysis. Kaplan-Meier survival estimates were compared with log-rank testing, while Cox-regression modeling was tested for prognostic factors in GS patients.

Results: The cohort included 26 primary gliosarcoma (PGS) patients (3.8%) and 7 secondary gliosarcoma (SGS) patients (1.0%). Compared to conventional GBM tumors, PGS tumors were significantly more often MGMT-unmethylated (73.9%) and located in the temporal lobe (57.7%). GS tumors often presented dural contact, while extracranial metastasis was only found in 1 patient. No significant differences were found between PGS and conventional GBM in progression-free-survival (6.8 and 7.6 months, respectively, $p = 0.105$) and in overall survival (13.4 and 15.7 months, respectively, $p = 0.201$). Survival following recurrence was not significantly different between PGS, SGS, and GBM. Temporal tumor location and MGMT status were found associated with PGS survival ($p = 0.036$ and $p = 0.022$, respectively).

Conclusion: Despite histopathological and location difference between GS and GBM tumors, the patients present similar survival outcome from standardized treatment. These findings support continued practice of radiation and temozolomide for GS patients.

Diagnosis of Gliosarcoma

According to the new World Health Organization (WHO) classification gliosarcoma is defined as a glioblastoma variant characterised by a biphasic tissue pattern with alternating areas displaying glial and mesenchymal differentiation. Invariably the clinical history of the patient is short and the presenting symptoms depend upon the location of the tumour. The aetiology of gliosarcoma remains speculative although it is recognised that gliomas can induce sarcomatous transformation in the supporting mesenchymal elements and irradiation of the central nervous system can induce malignant transformation of the brain parenchyma and the meninges predominantly to fibrosarcoma.

Treatment of Gliosarcoma

There are important first steps a patient must take in order to maximize the chances of survival and a successful therapy.

First one needs to clarify and confirm the pathologic diagnosis. This pathologic diagnosis is made based on the tissue obtained from the initial surgery. Going forward, the treatment plan will be created based on this diagnosis. This formal diagnosis is made by the neuro-pathologists and is the most important piece of information of any treatment plan.

It is important to note that it is critical to save all tumour tissue collected at the initial surgery. Not only for pathologic diagnosis but also many clinical trials down the road will require frozen tissue from the initial surgery.

Next one wants to make sure the pathology diagnosis matches what one sees on the MRI scan and what is going on with the patient. Taking all of these data points into consideration helps one get a better picture of what is going on with the patient, and can help to better determine how to move forward.

Once one is sure about the diagnosis one can move forward with Treatment Options. Sometimes the treatment will include a more extensive surgery in order to maximise the total resection of the tumour. In higher grade tumours, treatment options can include Radiation Therapy alone, combination therapy of Radiation and Chemotherapy, or combination therapy of Radiation and Chemotherapy followed by additional Chemotherapy.

The decision of what therapy to administer is provided by the Neuro-Oncologists.

If traditional therapy fails in the newly diagnosed setting, additional therapy can be administered in the recurrent setting.

The treatment approaches in the recurrent setting mirror some of the options in the newly diagnosed setting. For example, one will need to identify if the patient needs additional surgery for de-bulking or further tumour resection. The neuro-oncologist will also need to identify if further radiation is needed. Most of the time in these recurrent settings additional systemic treatment will need to occur. These forms of treatment can be either standard chemotherapy agents or experimental therapies as part of an ongoing clinical trial.

Because each patient's treatment plan is unique, therapy normally is dictated by several factors including a person’s age, Karnofsky Score and any previous therapy they have received. Advances in molecular diagnostics laboratory is enabling one to better predict what agents will benefit a particular patient group. In general, the following is an overview of agents used to treat Gliosarcoma patients. This list includes all patients treated at UCLA Neuro-Oncology between 1/16/2015 and 1/16/2017.

Chemotherapy Agents:

- Accutane
- Avastin (Bevacizumab)
- BiCNU Carmustine
- Carboplatin
- CCNU Lomustine

- CPT -11 (CAMPTOSAR, Irinotecan)
- Etoposide (Eposin, Etopophos, Vepesid)
- TEMODAR

Ma, R., Alexe, D-M. & Pereira, E.A. 2020.
Background: Gliosarcomas are malignant tumors of the central nervous system. As a variant of glioblastomas (GBM), they are treated in a similar fashion. However, there is growing evidence to suggest that they may be a separate entity.
Methods: Due to the rarity of primary gliosarcomas (PGS), here we publish data from a single center spanning over 14 years, comprising possibly one of the biggest case series in the literature to our knowledge.
Results: The mean age at presentation was 59 years with male preponderance (1.75:1). The most common presenting symptoms were balance and mobility issues (61%), followed by headaches (50%) and visual problems (39%). Tumours were most likely to involve the frontal and parietal lobes (27% and 21% respectively). Patients under 50 had a significant survival advantage (50% versus 32%). All patients had surgery, 79% had adjuvant radiotherapy, with a further 21% also receiving chemotherapy. Median survival from surgery of patients diagnosed with PGS was 6.6 months. Median and one-year survival were significantly better for patients who received radiotherapy (14 months; 46% one year survival) and improved further with combined radio- and chemotherapy (30 months; 77%, one year survival).
Conclusions: For patients of good functional status, adjuvant chemo-radiotherapy is warranted and should be offered as it confers a much-improved overall survival.

Jin, M.C., Liu, E.K., Shi, S., Gibbs, I.C., Thomas, R., Recht, L., Soltys, S.G., Pollom, E.L., Chang, S.D., Hayden, G. M., Nagpal, S. & Li, G. 2020.
Introduction: Gliosarcomas are clinically aggressive tumors, histologically distinct from glioblastoma. Data regarding the impact of extent of resection and post-operative adjuvant therapy on gliosarcoma outcomes are limited. **Methods:** Patients with histologically confirmed gliosarcoma diagnosed between 1999 and 2019 were identified. Clinical, molecular, and radiographic data were assembled based on historical records. Comparisons of categorical variables used Pearson's Chi-square and Fisher's exact test while continuous values were compared using the Wilcoxon signed-rank test. Survival comparisons were assessed using Kaplan-Meier statistics and Cox regressions. **Results:** Seventy-one gliosarcoma patients were identified. Secondary gliosarcoma was not associated with worse survival when compared to recurrent primary gliosarcoma (median survival 9.8 [3.8 to 21.0] months vs. 7.6 [1.0 to 35.7], p = 0.7493). On multivariable analysis, receipt of temozolomide (HR = 0.02, 95% CI 0.001-0.21) and achievement of gross total resection (GTR; HR = 0.13, 95% CI 0.02-0.77) were independently prognostic for improved progression-free survival (PFS) while only receipt of temozolomide was independently associated with extended overall survival (OS) (HR = 0.03, 95% CI 0.001-0.89). In patients receiving surgical resection followed by radiotherapy and concomitant temozolomide, achievement of GTR was significantly associated with improved PFS (median 32.97 [7.1-79.6] months vs. 5.45 [1.8-26.3], p = 0.0092) and OS (median 56.73 months [7.8-104.5] vs. 14.83 [3.8 to 29.1], p = 0.0252). **Conclusion:** Multimodal therapy is associated with improved survival in gliosarcoma. Even in patients receiving aggressive post-operative multimodal management, total surgical removal of macroscopic disease remains important for optimal outcomes.

Srivastava, H., Dewan, A., Sharma, S.K., Negi, P., Dewan, A.K., Parricha, S. & Mehrotra, K. 2018.
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.

Prognosis (Outlook) of Gliosarcoma
Gliosarcoma is a rare primary malignant tumour of the central nervous system with poor prognosis. The median survival time of this disease ranges from 6 months to 14.8 months. However, a computer literature search indicated few long-term survivors. There is a case of a survivor of Gliosarcoma with radiation-induced meningeal sarcomas, who showed no indication of recurrence for more than 9 years.

Smith, D.R., Wu, C.C., Saadatmand, H.J., Isaacson, S.R., Cheng, S.K., Sisti, M.B., Bruce, J.N., Sheth, S.A., Lassman, A.B., Iwamoto, F.M., Wang, S.H., Canoll, P., McKhann, G.M. 2nd, & Wang, T.J.C. 2018.
"Gliosarcoma is a rare histopathologic variant of glioblastoma traditionally associated with a poor prognosis. While gliosarcomamay represent a distinct clinical entity given its unique histologic composition and molecular features, its relative prognostic significance remains uncertain. While treatment of gliosarcoma generally encompasses the same standardized approach used in glioblastoma, supporting evidence is limited given its rarity. Here, we characterized 32 cases of gliosarcoma and retrospectively evaluated survival relative to 451 glioblastoma patients diagnosed during the same era within the same institution. Overall, we identified 22 primary gliosarcomas, representing 4.7% of WHO Grade IV primary glioblastomas, and 10 secondary gliosarcomas. With median age of 62, patients were predominately Caucasian (87.5%) and male (65.6%). Tumors with available molecular profiling were primarily MGMT-unmethylated (87.5%), IDH-1-preserved (100%) and EGFR wild-type (100%). Interestingly, while no significant median survival difference between primary gliosarcoma and glioblastoma was observed across the entire cohort (11.0 vs. 14.8 months, $p = 0.269$), median survival was worse for gliosarcoma specifically among patients who received modern temozolomide-based (TMZ) chemoradiotherapy (11.0 vs. 17.3 months, $p = 0.006$). Matched-pair analysis also trended toward worse median survival among gliosarcomas (11.0 vs. 19.6 months, log-rank $p = 0.177$, Breslow $p = 0.010$). While adjuvant radiotherapy (HR 0.206, $p = 0.035$) and TMZ-based chemotherapy (HR 0.531, $p = 0.000$) appeared protective, gliosarcoma emerged as a significantly poor prognostic factor on multivariate analysis

(HR 3.27, p = 0.012). Collectively, our results suggest that gliosarcoma may still portend worse prognosis even with modern trimodality therapy."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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