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Prognosis and management of gliosarcoma patients: A review of literature

Fadi Saadeh[a], Sarah El Iskandarani[a], Marwan Najjar[b], Hazem I. Assi[c,*]

[a] American University of Beirut, Faculty of Medicine, Beirut, Lebanon
[b] American University of Beirut Medical Center, Department of Surgery, Beirut, Lebanon
[c] American University of Beirut Medical Center, Department of Internal Medicine, Hematology and Oncology, Naef K. Basile Cancer Institute, Beirut, Lebanon

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ABSTRACT

Gliosarcoma (GSM) is a variant of glioblastoma (GBM), the most common primary malignant brain tumor that occurs in adults. GSM is characterized by its biphasic components: the gliomatous and sarcomatous components and categorized into primary and secondary GSM. Intrinsic to the brain parenchyma, GSM is usually managed by gross total resection, and radiotherapy with/without chemotherapy. While the benefits of treatment remain unclear, cases have always been managed similar to GBM cases yielding different treatment outcomes between the two groups. The scarcity of research done on GSM suggests that further investigation is needed. Genetic studies on tumor samples and an in-depth examination of tumor subtypes and categories could result in identification of certain targetable alterations. The objective of this review is to summarize the available findings on characteristics, prognosis and management of GSM patients.

1. Introduction

Glioblastoma (GBM) is the most prevalent primary malignant brain tumor that occurs in adults, accounting for almost half of brain tumor cases [1]. Gliosarcoma (GSM), a variant of GBM, is a malignant tumor that arises from glial cells and is characterized by its biphasic components: gliomatous and sarcomatous [2,3]. Gliosarcoma is further categorized into primary and secondary GSM, after prior GBM diagnosis [4]. In clinical practice, GSM and GBM are managed and treated similarly, although several studies have shown different outcomes when these tumors are identically treated [5,6]. The available studies on GSM remain very few due to the scarcity of cases, and further investigation is still needed. In order to highlight the necessity of further inquiry in this field, this review summarizes the available findings and treatment options, characteristics and prognoses of patients with GSM.

2. Methods

2.1. Search strategy and study selection

We conducted updated searches to identify published case reports, case series, reviews, retrospective studies and randomized controlled trials (RCTs), including Cochrane, MEDLINE and PubMED up to January 2019. Ongoing clinical trials were retrieved from www.clinicaltrials.gov. Search was limited to manuscripts written in English only. Main search terms used were: high-grade glioma, gliosarcoma, glioblastoma, glioma and brain neoplasms. Due to the scarcity of manuscripts on gliosarcoma and small populations per study, almost all English manuscripts were taken into consideration.

2.2. Data collection and analysis

Review authors screened the search results and reviewed the abstracts of potentially relevant articles before retrieving the full texts of eligible articles.

3. GBM/GSM characteristics and relation to prognosis

3.1. Subtypes

Two GSM subtypes have been identified and described, each having its own prognosis and treatment plan [7]. Sarcomatous predominant GSM is characterized by its similarity to meningioma, production of reticulin and lack of GFAP positivity; gliomatous predominant GSM is characterized by necrosis seen on pathological examination, lack of reticulin and expression of GFAP [7–9]. In both studies conducted by Han et al and Salvati et al., the sarcomatous subtype had better overall survival (OS): 16 vs. 9.6 months and 71 weeks vs. 63 weeks,

* Corresponding author at: Department of Internal Medicine, Hematology and Oncology, American University of Beirut Medical Center, PO Box 11 0236, Riad El Solh, 1107 2020, Beirut, Lebanon.
E-mail address: ha157@aub.edu.lb (H.I. Assi).

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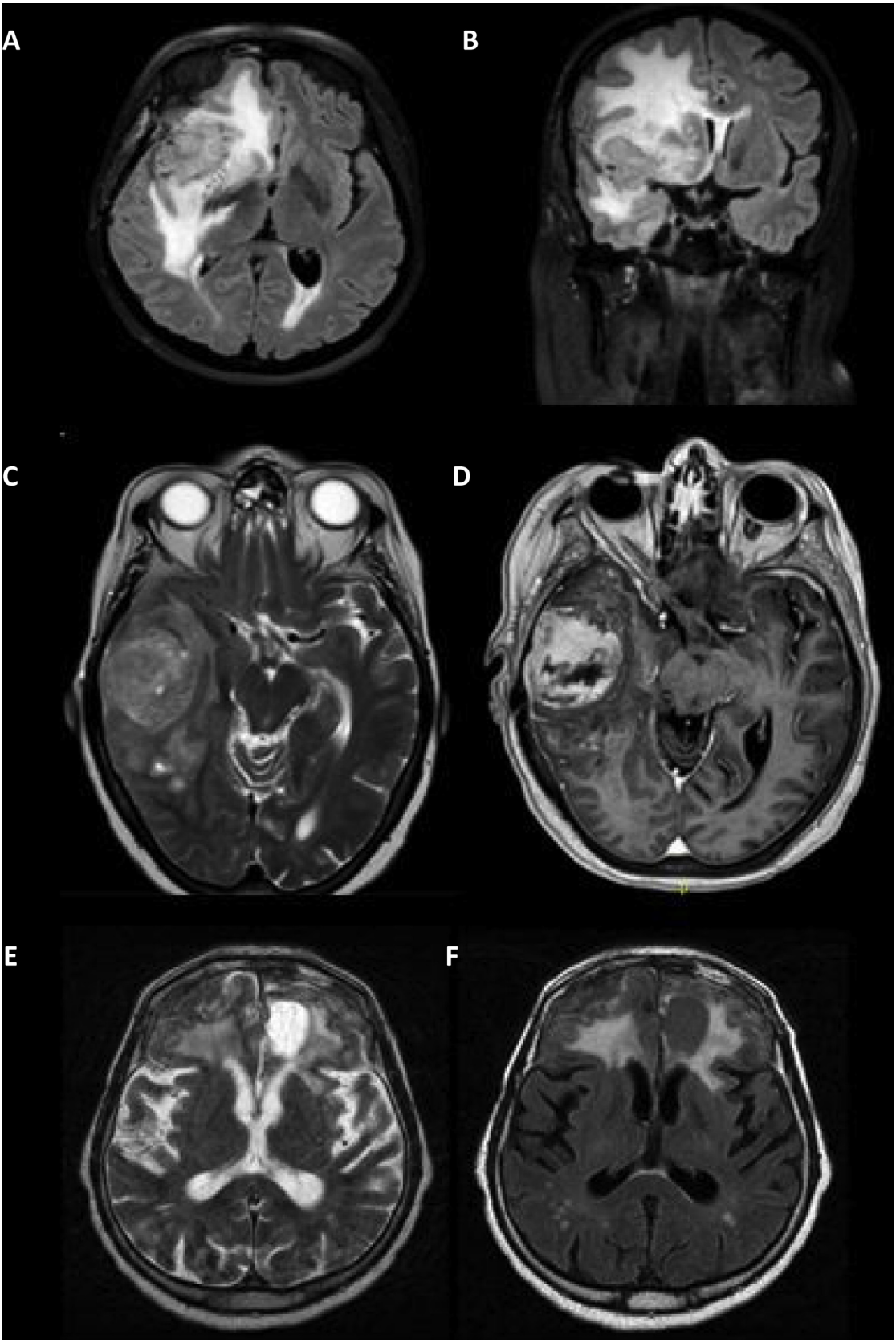

Fig. 1. MRI images showing different features of gliosarcoma. A–B) Sagittal image of the tumor (4.7 x 2.6 x 3.4 cm) in the right insular region after surgical biopsy. A midline shift and high FLAIR signal can be seen due to a combination of increased edema and prior radiation therapy. C–D) Heterogeneously enhancing mass is seen in the right temporal lobe measuring 4.5 x 3.7 cm, extending to the basal ganglia and frontoparietal region. An area of central necrosis can be seen along with significant mass effect on the right lateral ventricle and evidence of uncal herniation. E–F) Shows the tumor's status post craniotomy for resection of his high grade tumor. In the image, there is a 1 cm enhancing nodule in the left anterior aspect of the left insula and a 6 mm enhancing nodule in the right superior frontal gyrus suggestive of recurrence.

respectively [7,8]. The higher survival rate of the sarcomatous subtype may be attributed to the higher success of gross total resection in this subtype, which in turn correlates with overall survival [7,8]. Because sarcomatous GSM resembles meningiomas in terms of location and demarcation, radical surgical resection is more attainable. Gliomatous GSM occurs within the brain parenchyma and tends to be more challenging to completely resect [7]. For instance, in Salvati's study, gross total resection could be achieved in all four sarcomatous tumors and one-third of gliomatous tumors [7].

When surgical resection is deferred, sarcomatous GSM demonstrates a worse prognosis due to its resistance to alkylating chemotherapeutic agents when compared to the other subtype [8,10]. While gliomatous GSM seldom metastasizes extracranially and rarely disseminates into CSF, sarcomatous GSM shows a high propensity to metastasize [4]. In fact, histopathological analysis of metastatic tumors showed a pure sarcomatous component, which supports the claim that this component has a higher propensity for spreading hematogenously [11–15].

3.2. Genetics

Because GSM has long been considered as a variant of GBM, the treatment strategies for GSM have been similar to GBM [16]. However, several studies and case series report that the treatment response of each of GBM and GSM is not identical, suggesting the possibility of underlying differences between these two pathologies [17–19]. Thus, efforts have been put to study the genetic distinctions of GSM and GBM in an attempt to explain the differences in treatment outcomes and eventually develop the optimal treatment for each. A number of mutations and amplifications have been explored in GBM and GSM, both primary and secondary, but their significance remains unclear.

When compared to GBM, lack of EGFR amplification was common to GSM (39 vs. 4%, respectively) [20,21]. Otherwise, the genetic profile of GSM seems to be comparable to that of GBM [16].

MGMT methylation correlated to response to TMZ treatment in GBM patients harboring this alteration. Specifically, methylation prevents MGMT from repairing the antineoplastic effect of TMZ, thus destroying the tumor. This correlation has not yet been properly founded in GSM patients. Among the 26 cases studied by Lee et al (21 primary GSM, 4 secondary GSM, 1 radiation-induced GSM), MGMT methylation was found in 3 cases (11.5%): one primary GSM and two secondary GSMs [16]. Conversely, other studies such as the one conducted by Kang et al showed a higher percentage of GSM patients with MGMT methylation (50% of the 12 primary GSM patients) [22]. While GBM patients with methylated MGMT promoters had a significantly greater overall survival with TMZ treatment [23], MGMT methylation was not associated with increased progression-free survival (PFS) (10.6 vs 5.3 mo, p 0.47) or OS (13.3 vs 13.9 mo, p 0.59) in GSM patients [24].

IDH1 mutations were found in two cases (7.7%), a primary GSM (1/21) and a secondary GSM (1/4), but not in radiation-induced GSM [16]. Similarly, IDH1 and IDH2 were shown to be correlated with prognosis in IDH1-mutated GBM as compared to wild-type [25,26]. However, no prognostic significance has been found in GSM patients.

TP53 mutation, which is seen in many cancer types, is most common in secondary GSM (67%), followed by primary GSM (23%) and GBM (11%) [20]. Other alterations include PTEN mutations (37%) and homozygous p16 deletions (37%) [20].

3.3. Radiological features

Gliosarcoma can be characterized by specific radiological features when compared to glioblastoma. In his study, Yi et al. examined MRI images of 48 GSM patients. Several variables were more commonly found in GSM MRIs, when compared to GBM, including hemorrhage, salt-and-pepper sign, unevenly thickened walls with paliform patterns, intratumoral large feeding artery and eccentric cystic portion. While the existence of an eccentric cyst as a radiological feature held significance in univariate analysis, Cox regression did not show any prognostic association with radiologic features of GSM [27]. Some of these features were found on the MRIs of our patients diagnosed with Gliosarcoma (Fig. 1).

3.4. Overall survival

Several studies investigated the survival and prognosis of GSM patients. Prognosis of both GSM and GBM was shown to be poor with median survival of almost 9 months [3]. Median overall survival (OS) reached 17.5 months (PFS of 6.4 months) for GSM patients; however, authors attributed this improved survival to a selection bias [4]. When considering each of PGS and SGS, it seems that PGS had a better outcome than SGS with a median OS of 24.7 (PFS = 7 months) and 8.95 months (PFS = 3.1), respectively [4]. This could be explained by the additional burden of a prior tumor and aggressive therapy given to SGS patients.

3.5. Overall survival in relation to patient baseline characteristics

Several factors influencing the overall survival have been studied via bivariate and multivariate analyses. Kozac et al. concluded that age, extent of resection, and adjuvant radiotherapy (RT) were the most significant predictors of overall survival. On the other hand, gender seemed to have only a slight effect, with male patients' survival slightly better than that of females [3]. In another study conducted by Walker et al., a multivariate Cox regression analysis showed that overall survival decreased with advanced age at diagnosis (HR 1.02, 95% CI 1.0–1.03, $p < 0.0001$) and lack of radiotherapy (HR 2.5, 95% CI 1.5–4.2, $p < 0.0001$). Similarly, other factors were reported to influence prognosis, such as lack of surgical resection, race, gender and marital status [28]. When histology was added to the multivariate Cox model examining prognostic markers for GSM and GBM, age, tumor location, extent of surgery, and adjuvant RT were again significantly associated with overall survival. It was deduced that histology is an important predictor of survival with worse prognosis for GSM patients (HR 5 1.17, 95% CI, 1.05–1.31) [3]. Tumor location had a minimal effect on the overall survival in GSM and was limited to rare sites such as the ventricular system [3]. Ventricular tumors are most commonly accompanied by hydrocephalus that exacerbates a patient's quality of life and impact overall survival. In multivariate analysis, Kozak et al found that the extent of resection and adjuvant RT persisted as significant predictors of overall survival. However, tumor size and gender did not show a significant association with survival [3].

3.6. Metastasis

While extracranial metastases from cerebral gliomas, including GBM, are very rare, the propensity for gliosarcomas to metastasize has been well established [10]. Previously studied GSM metastatic foci contained both their gliomatous and sarcomatous components [29–31]. However, newer studies reported that upon pathological examination, metastatic foci were only of sarcomatous nature [11–13]. Such findings led to the conclusion that the sarcomatous component of GSM has a higher propensity to metastasize and disseminate hematogenously as compared to the gliomatous counterpart [10,14].

Extracranial metastases have been reported in 11% of gliosarcoma, most commonly involving the lungs (72%), liver (41%) and lymph nodes (18%), and less commonly the spleen, adrenal glands, kidneys, oral mucosa, skin, bone marrow, skull, ribs and spine [11–13,15,30,31]. In the case demonstrated by Beamont et al., metastatic foci were seen in at least 14 different sites — 6 of which not previously reported such as the thyroid, pericardium, myocardium, diaphragm, pancreas and stomach. This pattern of spread to the thorax, abdomen, bone and skin further elucidates the propensity of sarcomatous neoplasms to disseminate hematogenously [14]. The observation

of intravascular tumor emboli with corresponding parenchymal necrosis in the striatum of the liver and kidney further supports the hematogenous nature of dissemination [14]. Having described the high number of metastatic foci, Beaumont postulated that this may be due to the high dose of radiation that the patient received. Beaumont argues that despite the fact that aggressive treatment of GSM, including surgery, radiation and other therapies, may extend survival, it might as well increase the risk of metastasis by facilitating the metaplasia of the sarcomatous angioinvasive phenotype [14,32].

4. Treatment modalities

4.1. Radiotherapy

Several studies investigate the efficacy of radiotherapy in the treatment of GSM patients. A significant increase in overall survival, when compared to patients undergoing surgery only, was seen in 25 patients treated with adjuvant radiotherapy (46 vs. 13 weeks; $p = 0.025$) [18]. Similarly, in a study conducted by Castelli et al., it was concluded that surgery followed by radiotherapy offered a superior outcome than surgery alone [6]. In multivariate analysis, a high total dose of radiotherapy (minimum dose of 54 Gy) correlated with improved overall survival (HR = 0.97, $p = 0.007$). However, no reports concerning metastatic potential of heavily irradiated tumors were included in this study. While addition of chemotherapy failed to improve survival, it has been speculated that dose escalation of chemotherapeutic agents could still improve overall survival beyond that reached with RT and surgery [6]. The role of radiotherapy in the treatment of GSM was further emphasized in the large study conducted by Kozak et al [3]. The power of this study lies in the use of the SEER database that is able to provide data on a large number of patients with GSM. Despite the statistical significance and power of evidence, the authors postulated that several factors were not accessible such as details pertaining to chemotherapy, radiotherapy, disease severity and duration [3]. Han et al attributed the worse outcomes in SGS patients who had received radiotherapy and TMZ for GBM to the possible role of some characteristic mutations absent in primary GSM, such as MGMT or EGFR positivity [33]. This reasoning could not be confirmed since molecular profiles of GBMs and SGS were absent. This raised the need for detailed molecular analyses to identify the unique alterations and characteristics of those GBMs that recur as GSM. Other limitations of this study were the retrospective nature, heterogeneity of baseline characteristics and treatment modalities, and small sample size [33].

4.2. Surgery

The correlation of extent of tumor resection with enhanced overall survival of GSM patients has been a subject of interest in several studies. Zhang et al (2016) demonstrated that overall survival greatly improved with extent of resection (HR: 1.518) [34]. Similarly, in the study conducted by Lee et al, multivariate analysis showed that gross total resection, at tumor progression or recurrence, was an independent positive prognostic factor in GSM patients ($P = 0.0003$) [16]. Other studies as well concluded the favorable prognosis offered by radical resection along with radiotherapy to GSM patients [35,36].

Since GBM and gliosarcoma may not be readily differentiated on imaging, the microsurgical technique used is basically similar for both lesions, where the tumor may be initially debulked and then removed until normal surrounding tissue appears. Gliosarcomas, however, tend to be harder at surgery, and more attached or stuck to the surrounding dura, rendering the surgery more challenging.

Sample size was a limitation in several studies, rendering the correlation between surgical resection and overall survival insignificant. Cachia et al. reported that patients undergoing gross total resections (GTR) at the time of first diagnosis tended to have a greater overall survival than those having subtotal resections (STR)— 24.7 vs 10.1 months; however, such a finding failed to achieve significance due to the small sample size ($p = 0.2$) [4]. Likewise, in the study conducted by Castelli et al., although surgical removal improved outcome (14 vs. 10 months) when compared to biopsy alone, the correlation did not reach statistical significance ($p = 0.19$) due to small sample size [6]. Even-though statistically significant results were obtained, significance was lost with multivariate analysis [3].

4.3. Bevacizumab

Bevacizumab is a recombinant (93% human; 7% murine) monoclonal IgG1 antibody that binds selectively and with high affinity to VEGF receptors on endothelial cells. Such an interaction inhibits the proliferation of endothelial cells and formation of new vessels [37]. When bevacizumab was given as a treatment for human cancers, a significant anti-tumor activity was seen in colon, breast, pancreas and prostate cancer [37]. Metastatic disease progression was inhibited and microvascular permeability was reduced [38]. Being a highly vascularized tumor and known to produce many pro-angiogenic factors, GBM was thought as a good target for bevacizumab treatment [9,37]. It was also extrapolated that bevacizumab can play an essential role in hindering GBM, and possibly GSM progression. To validate this hypothesis, bevacizumab was given to PGS and SGS patients. PGS patients treated with bevacizumab had a PFS of 4.2 months from initiation of treatment and an OS of 8.4 months [4]. In SGS patients who received bevacizumab treatment at the time of diagnosis, PFS was 3.8 months and OS was 7.3 months from the start of treatment [4]. It was postulated by Cachia et al that the improved outcomes witnessed among the studied patients can be due to the administration of bevacizumab, specifically in patients with recurrent GSM. However, this improved outcome might have also been affected by the fact that the patients were sampled from a quaternary referral center and were already involved in clinical trials.

4.4. Chemotherapy

A number of chemotherapeutic agents have been used in the treatment of patients with GSM, and several studies were conducted to test the significance of the addition of chemotherapy in management of GSM. Even though some studies presented negative findings, other studies could shed light on the benefits of some chemotherapeutic agents. Some did not find any significant variation in OS when adjuvant chemotherapy was administrated [6]. Benefit was only seen with non-TMZ chemotherapy such as Cisplatin, Lomustine, and Cytarabine; however, such a conclusion needs further substantiation using a larger sample size [6].

4.5. Temozolomide (TMZ)

Some studies demonstrated benefit of TMZ as part of the therapy regimen, while others found no significant improvement in OS. In studies assessing the effect of TMZ on both GSM and GBM, Castelli et al concluded that the addition of chemotherapy to radiotherapy did not extend the OS in GSM patients; however, survival benefit was evident in GBM patients [6]. Authors attributed the difference in outcome to the distinct genetic profiles of both populations at hand [10]. Because of the low rate of MGMT methylation among patients with gliosarcoma, it was likely that GSM patients benefit much less from TMZ when compared to GBM patients, who harbor a higher frequency of MGMT methylation [5].

In studies that included GBM patients only, TMZ treatment led to decreased OS in those patients developing SGS (4.3 and 10.5 months, respectively; $p = 0.045$) [33]. This in turn highlights the presence of an underlying predisposition to poor response to chemotherapy in patients with SGS or PGS, and emphasizes a fundamental difference between GBM patients and those developing secondary gliosarcoma.

In studies limited to GSM patients only, different results were

reported concerning response to TMZ treatment. In Han et al.'s study, TMZ showed no benefit when given to patients harboring GSM, specifically PGS [8]. Although a study (n = 46 patients) showed an improvement in the 2-year OS with TMZ from 10.2% (without TMZ) to 20% (with TMZ), the result did not reach statistical significance [28]. Similarly, although the median OS increased from 14.5–16 months in patients treated by radiotherapy and TMZ when compared to radiotherapy alone, results failed to achieve statistical significance [7]. Salvati et al. claimed that despite the small sample size, the median survival rate of patients treated with TMZ was higher than that previously reported for any other chemo-radiotherapy regimen [7].

One study did show an improvement in OS with TMZ treatment. Adeberg et al. concluded that the addition of TMZ therapy to radiotherapy significantly improves overall survival (OS) in GSM patients as compared to cases receiving radiation therapy alone (13.9 vs. 9.9 months; p = 0.045), regardless of MGMT methylation [24].

Some studies explained the negative findings by the low rate of MGMT methylation that was postulated to be the reason behind the ineffectiveness of TMZ treatment in GSM [16]. Kang et al.'s conclusions were in accordance with this proposed explanation since GSM patients with MGMT methylation had longer overall survival when treated with TMZ; however, such findings cannot be generalized due to the small sample size [22]. Still, other studies showed that even TMZ therapy for tumors with MGMT methylation (n = 5) failed to show a significant correlation with either PFS (6 vs 7.8, p = 0.92) or OS (21.2 vs 21.9, p = 0.83) [24].

4.6. Immunotherapy

Few studies addressing immunotherapy for recurrent glioblastoma included patients with gliosarcoma. After its favorable response in increasing long term survival in high-grade gliomas including gliosarcoma (Phase I), a phase II trial of DNX-2401, an oncolytic adenovirus, along with Pembrolizumab, a PD-1 receptor blocker, is currently underway (CAPTIVE/KEYNOTE-192: NCT02197169). Sharing similar targets, another phase I/II trial addresses the efficacy of atezolizumab, a PD-L1 inhibitor in conjunction with temozolomide and radiotherapy (NCT03174197).

4.7. Combination therapy

Apart from single modality treatments, current guidelines set by the national comprehensive cancer network (NCCN) state that maximal safe surgical resection followed by RT along with concurrent and adjuvant TMZ is recommended for GSM treatment [39]. Therefore, several studies have been conducted to study the effect of multi-modality treatment on the outcome of GSM. In Castelli's study, 75 patients between the ages of 23–79 years were treated with a combination of surgery (n = 66), TMZ (n = 58) and radiotherapy (n = 72) [6]. OS of two years was achieved in 12% of the patients (95% CI 4–20%) and the median OS was 13 months [6].

Although the prognosis of GSM is known to be generally poor, multimodality treatment seems to extend survival [7]. In a study conducted by Salvati et al, treatment consisted of whole brain radiotherapy with ^{60}Co, and TMZ chemotherapy [7]. It was claimed that despite the insignificant results, chemotherapy (as shown by TMZ) seemed to add benefit to the OS when added to radiotherapy in both patients with sarcomatous and gliomatous gliosarcoma (median survival 69.5 weeks vs. 63 weeks in patients with postoperative radiotherapy alone). It was still suggested that patients treated with adjuvant TMZ may have a more prolonged survival than patients treated with surgery and radiotherapy alone [7]. However, it might be that the lack of significant results is due to the small sample population and not accounting for age as a confounding factor. In that, the group that received surgical treatments only, had the eldest patients (mean age 80 years) and the lowest OS. Thus, a correlation between OS and therapy regimen cannot be concluded.

Similarly, Kozak et al.'s epidemiological study demonstrated the positive outcome of multimodality treatment: tumor resection (not biopsy only) along with adjuvant RT correlated with an increase in OS [3]. In both GBM and GSM, it was found that the three variables most closely associated with survival were age, extent of resection, and adjuvant RT use. After correcting for postoperative mortality, the impact of adjuvant RT was reanalyzed with the exclusion of patients who survived less than 2 months after diagnosis, and adjuvant RT still demonstrated increased OS. Even when multivariate Cox proportional hazards models for GSM and GBM were done, adjuvant RT still remained one of the most significant predictors of overall survival for both GSM and GBM.

Conversely, in a study conducted by Alfredo et al, combined multimodal therapy did not show improvement in OS [40]. Surgical resection was performed with post-operative radiotherapy (completing a total mean dose of 5400 cGy) and weekly vincristine-based chemotherapy. No reasoning was provided by the authors to justify the use of vincristine-based chemotherapy instead of TMZ. None of the patients achieved a complete response in this study. Results were attributed to the inherent aggressive features of the tumor in the studied population [40].

5. Conclusion

The prognosis of GSM is related to a variety of factors. Age, extent of resection and adjuvant radiotherapy (RT) were shown to be significant predictors of overall survival. Several studies report a longer OS for GBM patients when compared to GSM. GSM subtypes also displayed differences in OS which affected the likelihood of tumor metastasis, response to treatment and candidacy for surgery.

As for treatment modalities, adjuvant radiotherapy seems to be crucial in improving OS, while keeping the metastatic potential of irradiated tumors within guard. The extent of tumor resection correlated with improved OS in several instances, yet not in all cases. Bevacizumab seems to be an approach that shows positive results; however, the scarce data impedes sound conclusions on this treatment method. Several studies investigated the efficacy of chemotherapeutic agents, most notably TMZ, as a modality of treatment for GSM, but its benefit remains unclear.

Despite the notable advances and improvement in OS, a consensus on the optimal treatment for GSM patients is unclear. While the scarcity of this tumor impedes the possibility of whole population genetic profiling, multicenter studies can provide enough data to identify genetic alterations specific to GSM and its subtypes, and target these alterations through different treatment modalities. This sheds light on the importance of conducting further studies to elucidate and explain the previously mentioned discrepancies in results, taking into consideration the limitations of the aforementioned studies.

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Statement of ethics

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