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RESEARCH

Molecular characterization of gliosarcoma reveals prognostic biomarkers and clinical parallels with glioblastoma

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Abstract

Purpose Gliosarcoma is a rare histopathological variant of glioblastoma, but it is unclear whether distinct clinical or molecular features distinguish it from other glioblastomas. The purpose of this study was to characterize common genomic alterations of gliosarcoma, compare them to that of glioblastoma, and correlate them with prognosis.

Methods This was a single-institution, retrospective cohort study of patients seen between 11/1/2017 to 1/28/2024. Clinical and genomic data were obtained from the medical record. Results were validated using data from AACR Project GENIE (v15.1-public).

Results We identified 87 gliosarcoma patients in the institutional cohort. Compared to a contemporary cohort of 492 glioblastoma, there was no difference in overall survival, though progression free survival was inferior for patients with gliosarcoma ($p = 0.01$). Several of the most-commonly altered genes in gliosarcoma were more frequently altered than in glioblastoma (*NF1*, *PTEN*, *TP53*), while others were less frequently altered than in glioblastoma (*EGFR*). *CDKN2A*/*CDKN2B*/*MTAP* alterations were associated with inferior survival on univariate Cox (HR = 5.4, $p = 0.023$). When pooled with 93 patients from the GENIE cohort, *CDKN2A/B* (HR = 1.75, $p = 0.039$), *RB1* (HR = 0.51, $p = 0.016$), *LRP1B* ($p = 0.050$, HR = 2.0), and *TSC2* (HR = 0.31, $p = 0.048$) alterations or loss were significantly associated with survival. These effects remained when controlled for age, sex, and cohort of origin with multivariate Cox.

Conclusion Gliosarcoma has a similar overall survival but worse response to treatment and different mutational profile than glioblastoma. *CDKN2A/B* loss and *LRP1B* alterations were associated with inferior prognosis, while *RB1* or *TSC2* alterations were associated with improved outcomes. These findings may have implications for clinical management and therapeutic selection in this patient population.

Keywords Prognostic marker · Molecular profiling · *CDKN2A/B* · Project GENIE · *LRP1B* · *TSC2*

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Introduction

Gliosarcoma is a rare and aggressive subgroup of glioblastoma characterized on histopathology by both glial and sarcomatous features [1, 2]. Gliosarcoma has a poor prognosis, with median overall survival of 9 months in a large, multicenter study [3]. This represents a similar or worse prognosis than that of other forms of glioblastoma [4]. Gliosarcoma can arise *de novo* as primary gliosarcoma or develop as secondary gliosarcoma following treatment of a pre-existing brain tumor. Primary gliosarcomas may have a more favorable prognosis than secondary gliosarcomas, though studies to date are based on very small populations [5]. Currently, standard management of gliosarcoma is identical to that of glioblastoma, consisting of maximal safe tumor resection and radiotherapy with concurrent and adjuvant temozolomide [6].

With the increased prevalence of next generation sequencing, common genomic alterations in glioblastoma and gliosarcoma have been identified. *EGFR* amplification, which occurs in approximately 40% of glioblastoma, is much less frequent in gliosarcoma, occurring in 0–20% of samples [7–16]. Conversely, *BRAF*, *TP53*, *PTEN*, *NF1*, and *TERT* alterations have been reported more frequently in gliosarcoma than glioblastoma [8, 9, 12–17]. While some genomic alterations are associated with prognosis in glioblastoma patients, it is unclear whether unique genomic alterations impact overall prognosis in gliosarcoma. Such knowledge is critical to guide clinical counseling and care management for patients and providers, particularly as new targeted therapies are being developed for gliomas. Here, we present the largest single-institution cohort of gliosarcoma patients who received a clinically standardized, large (> 400 genes) next-generation sequencing panel along with clinical outcome data. We characterize common genomic alterations and their impact on prognosis in the institutional cohort, then compare common alterations to those of glioblastoma and the large, publicly available Project GENIE database.

Methods

Data collection

A waiver of consent was obtained from the Johns Hopkins Institutional Review Board for this retrospective study (IRB00442172). Patient charts in the electronic medical records were searched for the key terms “gliosarcoma” or “glioblastoma, IDH-wildtype, WHO grade 4 with sarcomatous change” and date of surgery between 11/2017 and 02/2024. Pathology reports for these charts were manually reviewed, and patients with histopathological gliosarcoma were included.

Information on IDH-wildtype glioblastoma patients was obtained from an institutional registry of IDH-wildtype glioblastoma patients diagnosed between November 2017 and January 2024. Clinical, histopathologic, and molecular data in this database were obtained via review of electronic medical records. Pediatric patients under the age of 18 were excluded. Overall survival (OS) for both glioblastoma and gliosarcoma patients was calculated using time from histopathologic diagnosis to time of death as obtained from patient medical records and public databases. Progression-free survival (PFS) was calculated from time to diagnosis to date of first progression.

Genomic characterization of institutional patients

Clinical next-generation sequencing data was extracted from the electronic medical record for all glioblastoma and gliosarcoma samples assayed using the institutional next generation sequencing (NGS) Solid Tumor Panel, which sequences over 400 cancer-related genes for point mutations, small insertion/deletion mutations, and select copy number amplifications, as previously reported [18, 19]. If a patient had multiple samples sequenced, only sequencing from the earliest sample was included for analysis. Both single nucleotide alterations and copy-number alterations, if tested, were used to determine whether a gene was altered. Due to a high rate of co-alteration, *CDKN2A/CDKN2B/MTAP* was treated as a single locus during Cox modeling, and an alteration in any of the genes was considered an alteration at that locus.

AACR project GENIE data

Data from AACR Project GENIE Version 15.1-public was downloaded from Synapse (https://www.synapse.org/Synapse:syn7222066/wiki/405659), and gliosarcoma samples were identified by searching the “CANCER_TYPE_DETAILED” column for “Gliosarcoma”. Patients from our institution were excluded to prevent overlap between our institutional cohort and the GENIE cohort. Gliosarcoma samples with targeted sequencing were identified, and if more than one sample was sequenced from each patient, the earliest sample was selected for analyses. Samples with pathogenic *IDH1* or *IDH2* mutations were excluded.

Overall survival time was not available for public release from Project GENIE. Thus, OS was estimated by converting the age at specimen collection (given in years) and the age at last known contact (given in days) to months and then subtracting the former from the latter. Patients without exact ages for these events (those equivalent to < 18 or > 89 years

at the time) were dropped. Analysis of genomic data from Project GENIE was modified from the pipeline used for our institutional cohort to accommodate differences in the panels used by contributing institutions. Only genes that were tested in more than half of the samples were considered when determining the topmost altered genes. For Cox modeling, copy number alteration data was not available for all samples and genes, and was only considered for genes that are well-known and commonly tested for amplifications and deletions (*EGFR*, *PDGFRA*, *CDKN2A/B*). For these genes, if the gene was known not to be mutated but did not possess copy number alteration data, or vice versa, the alteration status of the gene was treated as missing data. Similarly, when *CDKN2A* and *CDKN2B* were combined into a single locus, if one gene was known to be unaltered and the other gene's alteration status was unknown, the alteration status of the locus was considered unknown. For this reason, *MTAP* was not included as part of the same locus as *CDKN2A/B*. *MTAP* was tested in only 11 out of 93 samples (11.8%), and its inclusion as part of the *CDKN2A/B* locus would have resulted in an unacceptably high proportion of missing data.

Table 1 Demographic characteristics of patients

Characteristic	Gliosarcoma (n = 87)	Glioblastoma (n = 492)	p-value
Sex			0.64
Male	54 (62.1%)	291 (59.1%)	
Female	33 (37.9%)	201 (40.9%)	
Age at diagnosis			
Median (IQR), years	60.4 (16.2)	65.0 (15.9)	0.0082**
18–35	0 (0%)	9 (1.8%)	
35–65	55 (63.2%)	237 (48.2%)	
>65	32 (36.8%)	246 (50.0%)	
Survival, available N			0.90
Deceased	56 (64.4%)	311 (63.2%)	
Alive	31 (35.6%)	181 (36.8%)	
Median overall survival, months (95% CI)	14.0 (12.9–17.4)	14.3 (13.0–15.9)	0.88
KPS			1.2e-8***
100	6 (6.9%)	42 (8.5%)	
90	26 (29.9%)	126 (25.6%)	
80	5 (5.7%)	67 (13.6%)	
<80	3 (3.4%)	126 (25.6%)	
Unknown	47 (54.0%)	131 (26.6%)	
MGMT Status			0.83
Methylated	14 (16.1%)	162 (32.9%)	
Unmethylated	24 (27.6%)	275 (55.9%)	
Indeterminate	3 (3.4%)	25 (5.1%)	
Not tested	46 (52.9%)	30 (6.1%)	
Resection			0.15
Gross total resection	18 (20.7%)	158 (32.1%)	
Subtotal resection	15 (17.3%)	160 (32.5%)	
Biopsy	2 (2.3%)	69 (14.0%)	
Unknown	52 (59.8%)	105 (21.3%)	
Known Treatment Status	51 (58.6%)	405 (82.3%)	
Received RT			
As First Line	51 (100%)	380 (93.8%)	0.096
At Least Once	51 (100%)	382 (94.3%)	0.094
Received TMZ			
As First Line	49 (96.1%)	350 (86.4%)	0.068
At Least Once	50 (98.0%)	357 (88.1%)	0.029*
Median Cycles of TMZ (IQR)	5 (2)	5 (3)	0.51

*p-value < 0.05. **p-value < 0.01. ***p-value <0.001.

Statistical analyses

All statistical analyses were performed using R statistical software, version 4.3.2 (R Foundation for Statistical Computing; www.rproject.org). Comparisons between glioblastoma and gliosarcoma were performed using two-sided Fisher's Exact test for categorical variables and two-sided Wilcoxon Rank Sum Test for continuous and ordinal variables. When comparing the frequency of gene alterations, p-values from Fisher's Exact Test were corrected for multiple testing using the Benjamini-Hochberg procedure. Visualization of genetic alterations was performed using the package 'ComplexHeatmap' (v2.18.0). All survival analysis was performed using the 'survival' (v3.5-7) and 'survminer' (v0.4.9) packages in R. Kaplan-Meier analysis, log-rank tests, and Cox proportional hazards models were performed with OS and PFS censored to 24 months. Missing values were dropped during Cox analysis.

Results

Patient demographics

We identified 87 patients with a pathological diagnosis of gliosarcoma in our institutional cohort. Of these, 51 had known treatment information while the remainder were lost to follow-up after surgery. 62.1% were male. Median age at diagnosis was 60.4 years (IQR 16.2 years; Table 1). The median overall survival (OS) was 14.0 months, and 64.4% of patients were deceased at the time of data collection. Of those patients with known baseline Karnofsky Performance Score (KPS; 46% of all patients), 92.5% had a KPS of 80 or above. Of the 40.2% of patients for whom extent of resection was known, 42.9% underwent subtotal resection while 51.4% received a gross total resection. Most (52.9%) patients were not tested for *MGMT* methylation status. Primary and secondary gliosarcoma did not differ significantly in sex, KPS, *MGMT* status, or extent of resection, though age at diagnosis was younger in patients with secondary gliosarcoma (Supplemental Table 1).

We also identified 492 IDH-wildtype glioblastoma patients. There were no significant differences between the gliosarcoma and glioblastoma patients in regards to age, extent of resection, or *MGMT* status, although the proportion of patients with known extent of resection and *MGMT* status was greater for glioblastoma (Table 1). However, patients with glioblastoma had a lower baseline KPS overall ($p < 0.0001$), with 25.6% of patients having a KPS under 80.

Treatment characteristics

Of the 87 gliosarcoma patients, 51 patients had known treatment status (58.6%). All 51 patients received at least one course of radiation therapy (RT), and all but one patient received temozolomide (TMZ) at least once (Table 1). The median number of adjuvant cycles of TMZ received was five. Gliosarcoma and glioblastoma did not significantly differ in the proportion of patients who received first-line RT or TMZ, although glioblastoma patients were less likely to receive TMZ at least once. Of the 405 (82.3%) glioblastoma patients with available treatment history, 93.8% received first line RT and 86.4% received first-line TMZ. When treated, the median number of cycles of TMZ were the same for patients with glioblastoma as that of gliosarcoma (5). There was insufficient data to compare subsequent lines of therapy including targeted therapies.

Genomic landscape of gliosarcoma

We examined the distribution of commonly altered genes in gliosarcoma. Among the 38 gliosarcoma samples that were sequenced with the NGS Solid Tumor Panel, 18 genes had an alteration frequency of greater than 10% (Fig. 1a). Over half of the patients in our cohort had alterations in *PTEN* (63%), *TERT* (55%), or *TP53* (55%). *CDKN2A* and *CDKN2B* were co-deleted in 6 patients (16%). Of these 6 patients, 5 also possessed a *MTAP* co-deletion. No tumors harbored pathogenic *IDH1* or *IDH2* mutations.

While the majority of sequenced gliosarcoma cases were identified as primary gliosarcomas ($n = 29$), several were identified at tumor recurrence as secondary gliosarcomas that had displayed other histology at initial diagnosis ($n = 7$). All but one of the secondary gliosarcomas had been diagnosed with glioblastoma at the time of initial encounter. The remaining patient was initially diagnosed with a high-grade CNS embryonal tumor, NOS. There were no significant differences in the frequency of common alterations between primary and secondary gliosarcomas (Supplemental Fig. 6).

We next evaluated whether the pattern of common genomic alterations in gliosarcoma was different from glioblastoma (Fig. 1b). We observed several differences. Notably, *EGFR* was more commonly altered in glioblastoma (p-adj = 0.00055) whereas *NF1*, *PTEN*, and *TP53* were more commonly altered in gliosarcoma (p-adj = 0.00055, 0.047, and 0.0035, respectively). In contrast to other published gliosarcoma cohorts, we identified no *BRAF* alterations in our cohort [8, 9, 15–17, 20, 21].

Survival characteristics in patients with gliosarcoma

We evaluated the prognostic impact of a histopathologic diagnosis of gliosarcoma. There were no statistically significant differences in OS between gliosarcoma and glioblastoma patients ($p = 0.95$), although primary gliosarcoma exhibited inferior progression-free survival compared to glioblastoma ($p = 0.0099$, Fig. 2, Supplemental Fig. 2). Additionally, there were no differences in OS between primary and secondary gliosarcoma patients when evaluating survival from time of first cancer diagnosis ($p = 0.38$; Supplemental Fig. 3). We observed that male sex and older age were associated with a worse outcome ($p = 0.065$, HR = 2.4; $p = 0.0053$, HR = 1.1, respectively; Fig. 3a, Supplemental Table 2). In our cohort, there was no survival impact of MGMT status, KPS, extent of resection, or primary versus secondary gliosarcoma, likely due to the limited sample size (Supplemental Table 2).

We then examined the association between specific genomic alterations and outcomes in our institutional cohort. We evaluated genes that were altered in more than 10% of patients. Among the 18 genes interrogated, only *CDKN2A*/*CDKN2B*/*MTAP* alterations showed a significant association with prognosis on univariate analysis ($p = 0.023$, HR = 5.4). *TSC2* alterations showed a trend towards being protective, but did not meet statistical significance ($p = 0.12$, HR = 0.31). These effects for *CDKN2A/CDKN2A/MTAP* ($p = 0.043$, HR = 4.8) and *TSC2* ($p = 0.14$, HR = 0.20) remained when controlling for *MGMT* methylation status, a well-known prognostic marker in glioblastoma and likely gliosarcoma, in a subgroup of 30 patients with known *MGMT* status [22, 23]. *RB1* alterations ($p = 0.036$, HR = 0.21) were also significantly associated with improved survival when controlling for *MGMT* status (Supplemental Fig. 4).

Impact of molecular alterations on survival in Project GENIE gliosarcomas

Recognizing that limited sample size impacted our analysis, we sought to validate our findings using a larger, independent cohort of gliosarcoma patients from AACR Project GENIE. We identified 93 gliosarcoma patients with both survival and sequencing data. This cohort did not differ significantly from our institutional cohort with regards to age, sex, or survival status (Supplemental Table 3). Extent

Fig. 1 Genomic features of gliosarcomas. (**A**) Co-mutation plot for all gliosarcoma samples with genomic profiling data (n=38) grouped by gliosarcoma type (primary vs. secondary). Genes altered in greater than 10% of samples and *IDH1/2* canonical alterations are shown in descending order of frequency. (**B**) Stacked barplots comparing gene alteration frequencies between glioblastoma (GBM) and gliosarcoma (GSM) for genes altered in greater than 10% of gliosarcoma samples. Benjamini-Hochberg adjusted p-values < 0.05 are displayed

of resection, KPS, *MGMT* status, and treatment information were not available. There was no significant difference in OS between our institutional and GENIE cohort using estimated OS for the GENIE cohort as described above (Supplemental Fig. 5).

Genomic alterations were similar between the institutional and GENIE cohort. As in our institutional cohort, *TERT*, *PTEN*, *TP53*, and *NF1* were the topmost altered genes in the GENIE cohort (Supplemental Fig. 6a). *RB1*, *CDKN2A*, and *CDKN2B* were also altered at high frequencies in both cohorts. There were no significant differences between the two cohorts in the alteration frequencies of the most commonly altered (> 10% of samples tested) genes in either cohort (Supplemental Fig. 6b).

Univariate Cox proportional hazards modeling was performed on the GENIE data set for age, sex, and the 18 genes identified in our institutional cohort. There was no effect from age or sex, unlike the institutional cohort. *CDKN2A/B* (p=0.096, HR=1.9) and *LRP1B* (p=0.043, HR=2.7) were associated with worse OS, while *RB1* (p=0.015, HR=0.44) were associated with improved prognosis

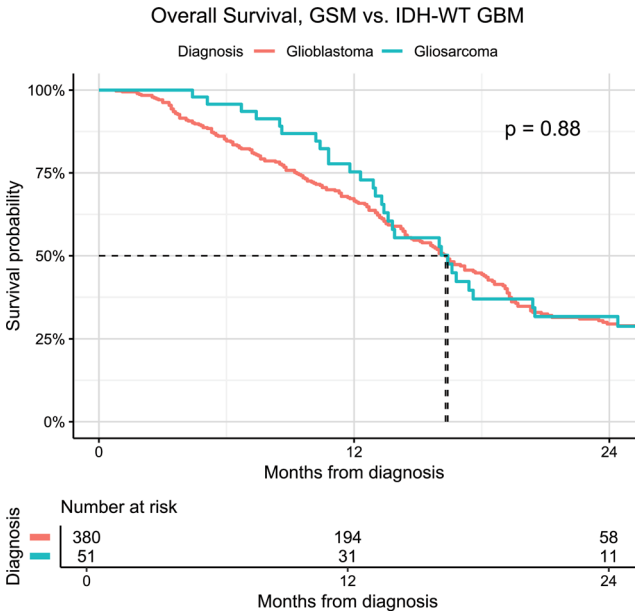

Fig. 2 Overall survival in gliosarcoma (GSM) versus glioblastoma (GBM). Kaplan-Meier and log-rank test of patients who received temozolomide or radiotherapy as part of first-line treatment for each group are included. Median overall survival is represented as dashed lines for each group

(Fig. 3b, Supplemental Table 4). Of note, the direction of effect was preserved between the two cohorts for multiple genes.

Impact of molecular alterations on survival in gliosarcoma in pooled data

We next performed pooled analysis using both cohorts to determine the effect on univariate cox analysis (Fig. 3c, Supplemental Table 5). As expected, *CDKN2A/B* ($p = 0.039$, HR = 1.8), *RB1* ($p = 0.016$, HR = 0.51), and *LRP1B* ($p = 0.050$, HR = 2.0), which were significant in at least one of the cohorts and had consistent directionality, were significantly associated with survival. *CDKN2A/B* loss and *LRP1B* alterations were associated with inferior survival, while *RB1* alterations were protective. Furthermore, *TSC2*, which was not significant in either cohort individually, was significantly associated with better prognosis in the combined data ($p = 0.048$, HR = 0.31). Kaplan-Meier curves of the pooled patients stratified by *CDKN2A/B*, *LRP1B*, *RB1*, and *TSC2* alteration status are shown in Fig. 3d-g.

We also fit multivariate Cox proportional models to the pooled data to determine whether associations between *CDKN2A/B*, *LRP1B*, *RB1*, and *TSC2* and survival remained after controlling for demographic variables. The effects of each gene were preserved when individually fit with age, sex, and cohort of origin (i.e. either institutional or GENIE); *CDKN2A/B* ($p = 0.021$, HR = 2.2) and *LRP1B* ($p = 0.024$,

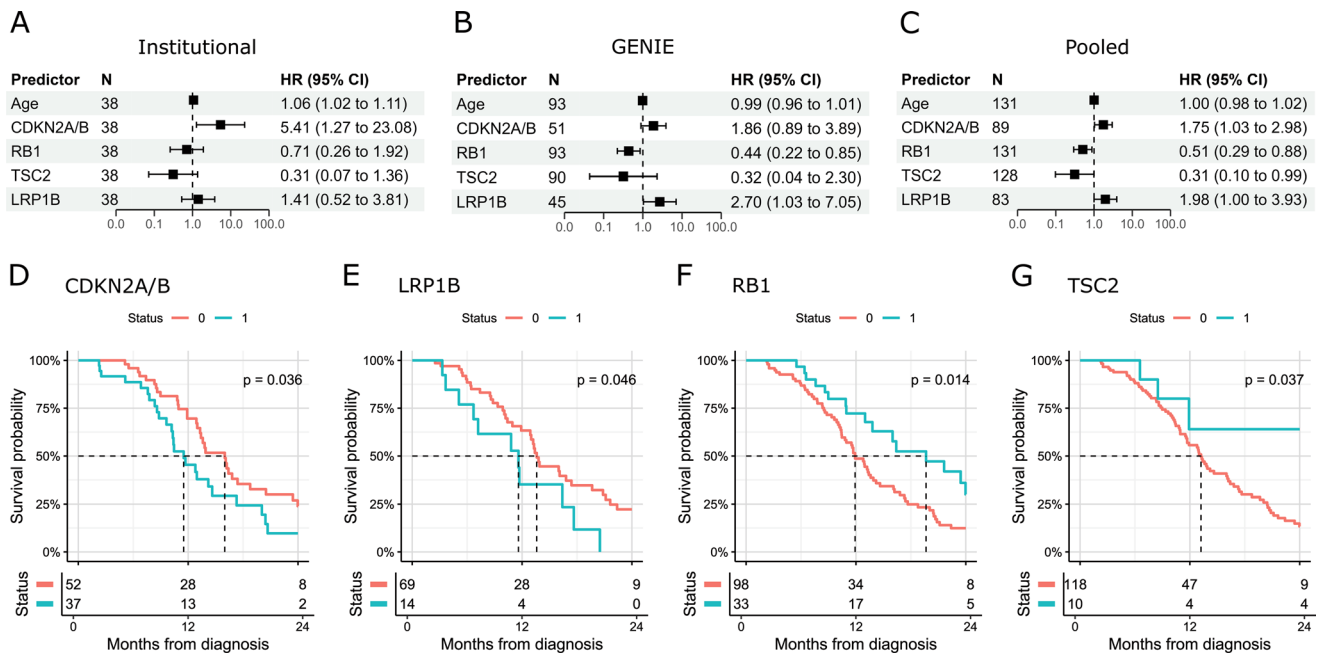

Fig. 3 Genetic factors impacting survival in gliosarcoma. (**A**-**C**): Univariate Cox proportional hazards results for select variables for the (**A**) institutional, (**B**) Project GENIE, and (**C**) pooled cohorts. Hazards ratios (HR) and 95% CI displayed for all comparisons. (**C**-**D**): Kaplan-Meier curves and log-rank test for pooled gliosarcoma patients from both cohorts stratified by *CDKN2A/B*, *LRP1B*, *RB1*, or *TSC2* alteration status. Median overall survival is represented as dashed lines

HR = 2.2) remained significantly associated with shorter survival, while *RB1* ($p = 0.011$, HR = 0.47) and *TSC2* ($p = 0.030$, HR = 0.27) remained associated with improved survival (Supplemental Fig. 7).

Discussion

Gliosarcoma is a rare histopathological subgroup of glioblastoma, but it has been unclear whether unique genetic alterations contribute to its appearance and clinical trajectory. Here, we characterized common genomic alterations in gliosarcoma, compared their frequencies in gliosarcoma and glioblastoma, and determined their effect on the survival of patients with gliosarcoma. We identified 18 genes altered in more than 10% of gliosarcoma patients. Of these genes, *PTEN*, *TP53*, and *NF1*were altered more frequently in gliosarcoma than glioblastoma while *EGFR* was altered less often. On univariate Cox, older age and *CDKN2A/CDKN2B/MTAP* alterations were significantly associated with worse outcome. We validated the direction of effect for *CDKN2A/B* but not age in an independent cohort of gliosarcoma patients from Project GENIE. Additionally, analysis of GENIE patients found *RB1* and *LRP1B* to be significantly associated with prognosis. A pooled analysis identified *CDKN2A/B* and *LRP1B* alterations were significantly associated with shorter survival, while *RB1* and *TSC2* alterations were associated with improved survival.

The commonly altered genes and relative frequency compared to glioblastoma were similar in our cohort to prior smaller cohorts. Namely, *EGFR* alterations were found at a lower frequency while *TP53*, *PTEN*, and *NF1* alterations were found at a higher frequency in gliosarcoma than glioblastoma [7–17]. Several topmost altered genes in our cohort, including *RB1*, *CDKN2A*, and *CDKN2B*, were also altered at high frequencies in previous studies [8, 10, 11, 14, 17]. Notably, our cohort did not identify any *BRAF* alterations, contrasting with reports of *BRAF* mutation frequencies of 7–22% [8, 9, 15–17, 20, 21]. We also observed a lower frequency of *TERT* promoter alterations (56%) than previous studies (72–87%), likely due to the fact that TERT promoter alterations were not identified in the institutional NGS Solid Tumor clinical reports until 2019, so it is likely underreported. Both these discrepancies may also be due to the high variance inherent to the small sample sizes of these studies ($n = 9$–45). Additionally, some of the most-altered genes in our cohort have not been previously reported.

The effect of genomic alterations on prognosis in gliosarcoma has been insufficiently evaluated in prior studies due to the rarity of gliosarcoma and limited cohort size. Our study identified multiple alterations associated with survival. We identified loss of *CDKN2A/B* as an indicator of inferior prognosis in our individual and pooled cohorts. This observation is consistent with many prior studies in IDH-wildtype glioblastoma as well as IDH-mutant astrocytoma and BRAF-altered glioma [2, 24]. Additionally, we observed alterations in *RB1* and *TSC2* as associated with improved survival. *RB1* loss is generally mutually exclusive with *CDKN2A/B* in glioblastoma, is associated with improved survival, and may have implications for therapeutic options [25–29]. Neither *LRP1B* nor *TSC2* are frequently altered in glioblastoma nor well characterized as unique contributors to outcome [30].

The unique alteration frequencies displayed by gliosarcoma may provide direction for the development of targeted therapies. EGFR inhibitors, which have been heavily investigated in glioblastoma but have thus far failed to demonstrate efficacy, are unlikely to be important treatment options in gliosarcoma given its low frequency of *EGFR* alterations [31–33]. By contrast, the high frequency of *NF1* alterations points to potential promise for NF1-targeted therapy. Preclinical, case studies, and early phase clinical studies of *NF1*-mutant glioblastoma have demonstrated sensitivity to MEK inhibitors, which may be translatable to gliosarcoma [34–38].

Despite the differences in gene alterations and their implications for survival, there were no overall differences in clinical outcome between patients with gliosarcoma and glioblastoma. Our clinical cohorts were not identical, as baseline performance status was higher and age at diagnosis was lower in patients with gliosarcoma, which may confound survival comparison. Prior studies have not clearly identified differences in survival between gliosarcoma and glioblastoma and survival for both cohorts in our study is within the reported range [29–31]. We did, however, identify differences in progression free survival, as patients with gliosarcoma had a worse progression free survival compared to those with glioblastoma. These findings further demonstrate the need for therapeutic advances for both of these patient groups.

Our analysis was limited by several factors. While our cohorts are some of the largest reported, the sample size of our institutional cohort, missing MGMT promoter methylation status from a subgroup, and the lack of precise OS data from Project GENIE still impose limitations. Additionally, as a retrospective study, our report is dependent on the availability and quality of data in the medical record. Finally, gliosarcoma is a histopathological diagnosis and at risk for inter-observer variability as genetic analyses, including methylation profiling, have been unable to reliably distinguish gliosarcoma thus far [38].

Here, we have demonstrated that patients whose tumors have a histopathological diagnosis of gliosarcoma are clinically similar to those with glioblastoma. However,

differences in genomic alterations may confer unique prognostic implications for those with gliosarcoma. Further investigation is needed to identify whether there are therapeutic implications to these differences as well.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11060-024-04859-0.

Author contributions E.R., L.C., K.S., and M.H. contributed to the study conception and design. Data acquisition, as well as administrative and technical support were performed by E.R., M.S., M.C., C.L., C.B., V.C., D.M., J.R.T., and D.K. Initial data processing was performed by M.C. Data analysis and interpretation was performed by L.C., P.H., K.S., and M.H. Statistical expertise was provided by P.H. The first draft of the manuscript was written by E.R., L.C., and K.S., and all authors provided editorial feedback to the manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request as participants were not consented for open data sharing.

Declarations

Ethics approval This study was approved by the Johns Hopkins Institutional Review Board (IRB00442172) on 4/29/2024.

Consent to participate A waiver of the HIPAA Privacy Authorization requirement was granted by the Johns Hopkins Institutional Review Board as part of the study approval process.

Consent to Publish Consent to publish was not obtained from participants. All identifying information has been removed.

Competing interests The authors declare no competing interests.

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