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Does location matter? Characterisation of the anatomic locations, molecular profiles, and clinical features of gliomas

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ABSTRACT

Introduction. Neuroanatomic locations of gliomas may influence clinical presentations, molecular profiles, and patients' prognoses.

Methods. We investigated our institutional cancer registry to include patients with glioma over a 10-year period. Statistical tests were used to compare demographic, genetic, and clinical characteristics among patients with gliomas in different locations. Survival analysis methods were then used to assess associations between location and overall survival in the full cohort, as well as in relevant subgroups.

Results. 182 gliomas were identified. Of the tumours confined to a single lobe, there were 51 frontal (28.0%), 50 temporal (27.5%), 22 parietal (12.1%), and seven occipital tumours (3.8%) identified. Tumours affecting the temporal lobe were associated with reduced overall survival when compared to all other tumours (11 months vs. 13 months, log-rank p = 0.0068). In subgroup analyses, this result was significant for males [HR (95%CI) 2.05 (1.30, 3.24), p = 0.002], but not for females [HR (95%CI) 1.12 (0.65, 1.93), p = 0.691]. Out of 82 cases tested for IDH-1, 10 were mutated (5.5%). IDH-1 mutation was present in six frontal, two temporal, one thalamic, and one multifocal tumour. Out of 21 cases tested for 1p19q deletions, 12 were co-deleted, nine of which were frontal lobe tumours. MGMT methylation was assessed in 45 cases; 7/14 frontal tumours and 6/13 temporal tumours were methylated.

Conclusion. Our results support the hypothesis that the anatomical locations of gliomas influence patients' clinical courses. Temporal lobe tumours were associated with poorer survival, though this association appeared to be driven by these patients' more aggressive tumour profiles and higher risk baseline demographics. Independently, female patients who had temporal lobe tumours fared better than males. Molecular analysis was limited by the low prevalence of genetic testing in the study sample, highlighting the importance of capturing this information for all gliomas.

Importance of this study. The specific neuroanatomic location of tumours in the brain is thought to be predictive of treatment options and overall prognosis. Despite evidence for the clinical significance of this information, there is relatively little information available regarding the incidence and prevalence of tumours in the different anatomical regions of the brain. This study has more fully characterised tumour prevalence in different regions of the brain. Additionally, we have analysed how this information may affect tumours' molecular characteristics, treatment options offered to patients, and patients' overall survival. This information will be informative both in the clinical setting and in directing future research.

Key words: glioma, glioblastoma, neuroanatomy, molecular profile, survival

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Introduction

The specific neuroanatomic location of tumours in the brain is thought to be predictive of patients' treatment options and overall prognosis [1–4]. Previous studies have demonstrated links between specific types and locations of tumours and clinical outcomes [4]. One study noted increased survival in patients with frontal lobe glioblastomas compared to temporal and parietal glioblastomas, and another study noted that gliomas that cross the midline tend to have poorer survival than those that do not [1, 2]. Low grade gliomas have been observed to more frequently involve functional regions of the brain than glioblastomas, and gliomas that do involve these regions tend to have poorer survival [5, 6]. Some research has pointed toward differing molecular signals in different anatomic regions of the brain as a potential mechanistic explanation for discrepancies in prevalence and survival [7].

Despite evidence for the clinical significance of this information, there is relatively little published research regarding the overall prevalence of tumours in the different anatomical regions of the brain. One study characterising the anatomic locations of 331 gliomas was published in 2007, but this study was conducted exclusively in Finland and did not examine clinical or molecular correlates [8]. A more recent study analysed an institutional cancer registry and identified racial background and tumour anatomic location as prognostic factors for glioblastoma patients [9]. This study only included one subtype of glioma and did not comment on molecular features of the tumours. Another recent study commented on the molecular signals of tumours in different regions of the brain and their correlations with patient survival. However, the authors focused on diffuse glioma and not the prevalence of primary brain tumours in these locations [7].

We used our institutional cancer registry to re-examine the hypothesis that anatomic location can be a prognostic factor in brain tumour cases. Additionally, we were able to more fully characterise tumour anatomic locations for all glioma grades and assess their molecular signatures and clinical characteristics, including overall survival (OS). We believe that reporting this information will help patients, healthcare providers, and neuro-oncology researchers better understand this disease and its clinical course.

Materials and methods

Study population

The Mayo Clinic Arizona Cancer Centre's institutional cancer registry was examined for glioma cases presented during a 10-year study period (2007–2017). Electronic medical records were reviewed to confirm that these were tissue-proven glioma cases as evidenced by pathology reports from surgical biopsy or resection. Patients for which no histopathological examination was completed were excluded from the study. Radiology reports and available CT and MRI images were reviewed by two members of the study team (CM and MMM) to record the specific neuroanatomical location of each primary tumour. Information about patient demographics (e.g. age, gender), clinical course, and tumour molecular biology was also recorded.

Statistical analysis

Categorical variables were described as count and percent, while continuous variables were described by their mean, standard deviation, median, and range. Demographic, clinical, and genetic characteristics were compared between gliomas of different anatomical locations. For continuous variables, Wilcoxon Rank Sum test was used when comparing two groups and ANOVA f-test when comparing three or more groups. Fisher's exact test was used to compare categorical variables between groups. Kaplan-Meier method and log-rank test were used to estimate and compare survival between glioma of certain anatomical locations at the univariate level. Multivariable Cox Proportional Hazard models where then built where log-rank test found significant results. Multivariable models were adjusted on clinically relevant variables. Univariate and multivariable models were repeated in gender subgroups. All hypotheses were two-sided with $p<0.05$ considered statistically significant. Analyses were performed in SAS v9.4 (SAS Institute; Cary, NC, USA).

Ethics

All patients included in this study signed informed consent to be included in the Mayo Clinic Arizona cancer registry for research purposes. Patients were approached for this at their initial presentation to the cancer centre. Patient information was maintained exclusively on a secure server and reviewed only by members of the study team. This research was approved by our institutional IRB.

Results

Anatomical locations

We identified a total of 182 tissue-proven glioma cases during the 10-year study period (Tab. 1). The mean age of study subjects was 61.4 years (range 4–91), and there were 109 males (59.9%) *vs* 73 females (40.1%) in the sample. The majority of the paediatric patients in the registry were excluded from the study because this population frequently receives treatment without tissue diagnosis (brainstem tumours). The five paediatric cases that were biopsy proven were included in our study. These included two thalamic tumours, one temporal lobe, one parietal lobe, and one frontal lobe tumour. Of the tumours that were located exclusively in one lobe of the brain, 51 were in the frontal lobe (28.02%), 50 were in the temporal lobe (27.47%), 22 were in the parietal lobe (12.09%), and seven were in the occipital lobe (3.85%)(Fig. 1). Other tumours involved multiple lobes of the brain, including nine fronto-parietal (4.95%), seven fronto-temporal (3.95%), and seven temporo-parietal

Table 1. Overall incidence of glioma by neuroanatomical location

Location	Frequency	Percentage
Frontal	51	28.0%
Temporal	50	27.5%
Parietal	22	12.1%
Multifocal	11	6.0%
Frontoparietal	9	4.9%
Frontotemporal	7	3.8%
Occipital	7	3.8%
Temporoparietal	7	3.8%
Thalamus	7	3.8%
Other*	4	2.2%
Brainstem	3	1.6%
Temporal, Frontal, Corpus Callosum	2	1.1%
Temporal, Parietal, Occipital	2	1.1%
Total	182	100%

*Four cases marked 'other' were: parietooccipital, cerebellum, intraventricular, and corpus callosum

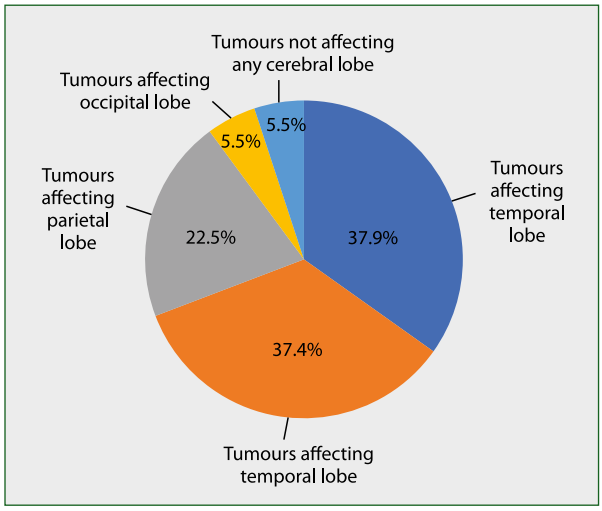


Figure 1. Involvement of cerebral lobes by gliomas; all gliomas affecting a particular lobe were counted for their respective category. Tumours affecting multiple lobes were included in multiple regions of the chart (e.g. frontotemporal tumours were counted as both 'frontal' and 'temporal')

tumours (3.85%). Eleven cases were multifocal in nature and not assigned a specific anatomical region (6.04%), and two tumours affected the temporal, parietal, and occipital lobes simultaneously (1.10%). Seven tumours were located in the thalamus (3.85%), and another seven were found in the brainstem or other locations within the CNS (3.85%). Eventually, 93 tumours were localised to the right side of the brain (51.1%), while 73 were localised to the left side (40.1%). The remaining 8.8% were midline tumours and/or tumours that involved structures in both hemispheres of the brain.

Survival analysis

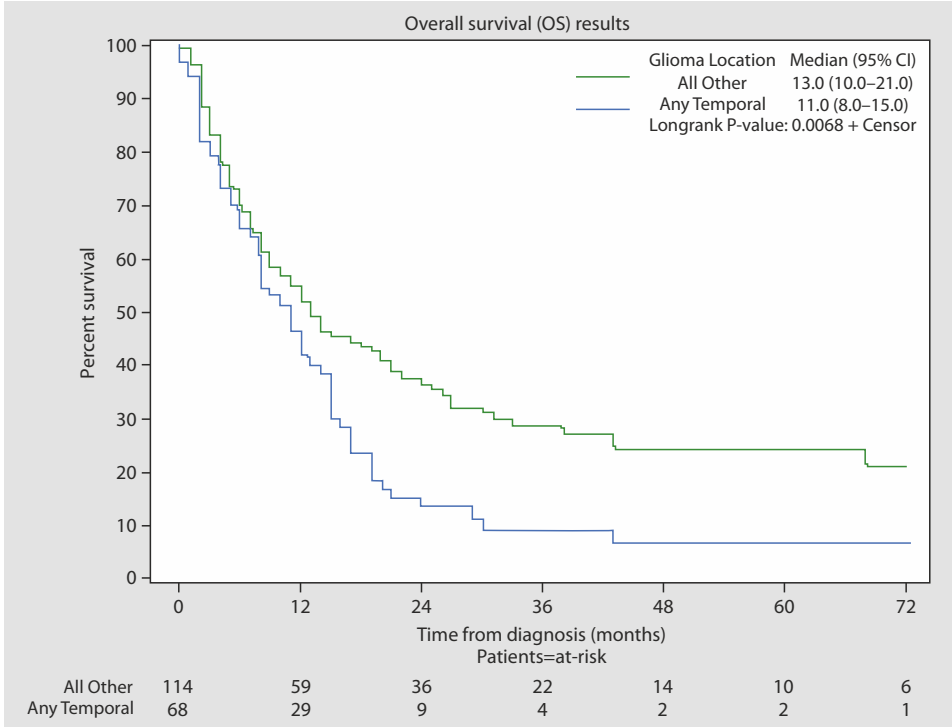
Patient overall survival (OS) was analysed based on the anatomical locations of brain tumours. Tumours involving the temporal lobe were found to have a statistically significant reduction in overall survival when compared to all other tumours without adjustment (median survival time 11 months *vs* 13 months, p = 0.0068) (Fig. 2). Subgroup analysis revealed a gender-based discrepancy in this finding. When analysing only male participants, the poorer temporal survival was significant both univariately [HR (95%CI) 2.05 (1.30, 3.24), p = 0.002] and after adjustment for age, grade, and surgery type [HR (95%CI) 1.62 (1.01, 2.61), p = 0.0475]. In the female-only subgroup, the relationship was never significant: univariate [HR (95%CI) 1.12 (0.65, 1.93), p = 0.691], multivariable [HR (95%CI) 0.90 (0.48, 1.68), p = 0.741] (Fig. 3).

Analysis of survival for tumours involving the frontal lobe vs. all other tumours was not statistically significant (median survival time 12 months vs. 10 months, p = 0.3). Due to the high occurrence of multi-lobe and multifocal tumours, overall survival was also assessed in the most common multi-lobe presentations. Tumours affecting both frontal and temporal lobes had poor survival outcomes compared to temporal lobe only (HR = 1.58, Type 3 p = 0.028), while tumours affecting the frontal lobe only and tumours affecting neither the frontal nor temporal lobes had increased overall survival compared to temporal lobe only (HR = 0.63 and HR = 0.72, Type 3 p=0.028) (Fig. 4, 5). However, this result was not upheld when adjusting for age, grade, and surgical approach (Type 3 p = 0.55). Tumour laterality was not an independent predictor of survival.

Clinical characteristics

Of 182 cases, 98 underwent neurosurgical resection of their tumours (53.8%), while 84 did not undergo resection and diagnosis was proven with an excisional biopsy (46.2%). Of the 98 patients who underwent resective surgery, a total gross resection was achieved in 51 (60.7%), while the others underwent partial or subtotal section (39.3%). As expected, patients who underwent any resective surgery had a significantly improved median overall survival (24 months vs 6 months, p < 0.0001). Tumour grade at the time of diagnosis was also a statistically significant predictor of survival, with the 118 patients with grade 4 tumours at diagnosis (64.8%) having significantly shorter survival than those with grades 1–2 (10.4%) or grade 3 tumours at diagnosis (22.5%) (p < 0.0001).

Significant differences were not observed in the type of surgery between frontal and temporal tumour cases (Tab. 2). Of our 51 cases confined to the frontal lobe, 26 patients underwent resective surgery (51.0%) and in 16 of these total gross resection was achieved (61.5%). Of the 50 cases confined to the temporal lobe, 22 underwent resective surgery (44.0%), and in 17 of these cases gross total resection was achieved (60.7%). Of the seven tumours affecting both the frontal and temporal lobes, none underwent resective surgery.



	Event/ /Total	Median (95% CI)[1]	Hazard Ratio (95% CI)[2]	Survival Estimates (95% CI)[1]	P-value
Overall Survival (OS) Results					
Glioma Location					0.0068*
All Other	81/114	13.0 (10.0–21.0)	0.63 (0.45–0.89)	12 Months: 52.0 (43.5–62.3%) 24 Months: 36.6 (28.5–47.0%) 36 Months: 28.7 (21.0–39.1%) 60 Months: 24.4 (17.1–35.0%)	
Any Temporal	58/68	11.0 (8.0–15.0)	Reference	12 Months: 41.8 (31.4–55.8%) 24 Months: 13.4 (7.1–25.4%) 36 Months: 8.9 (3.8–21.0%) 60 Months: 6.7 (2.4–18.7%)	

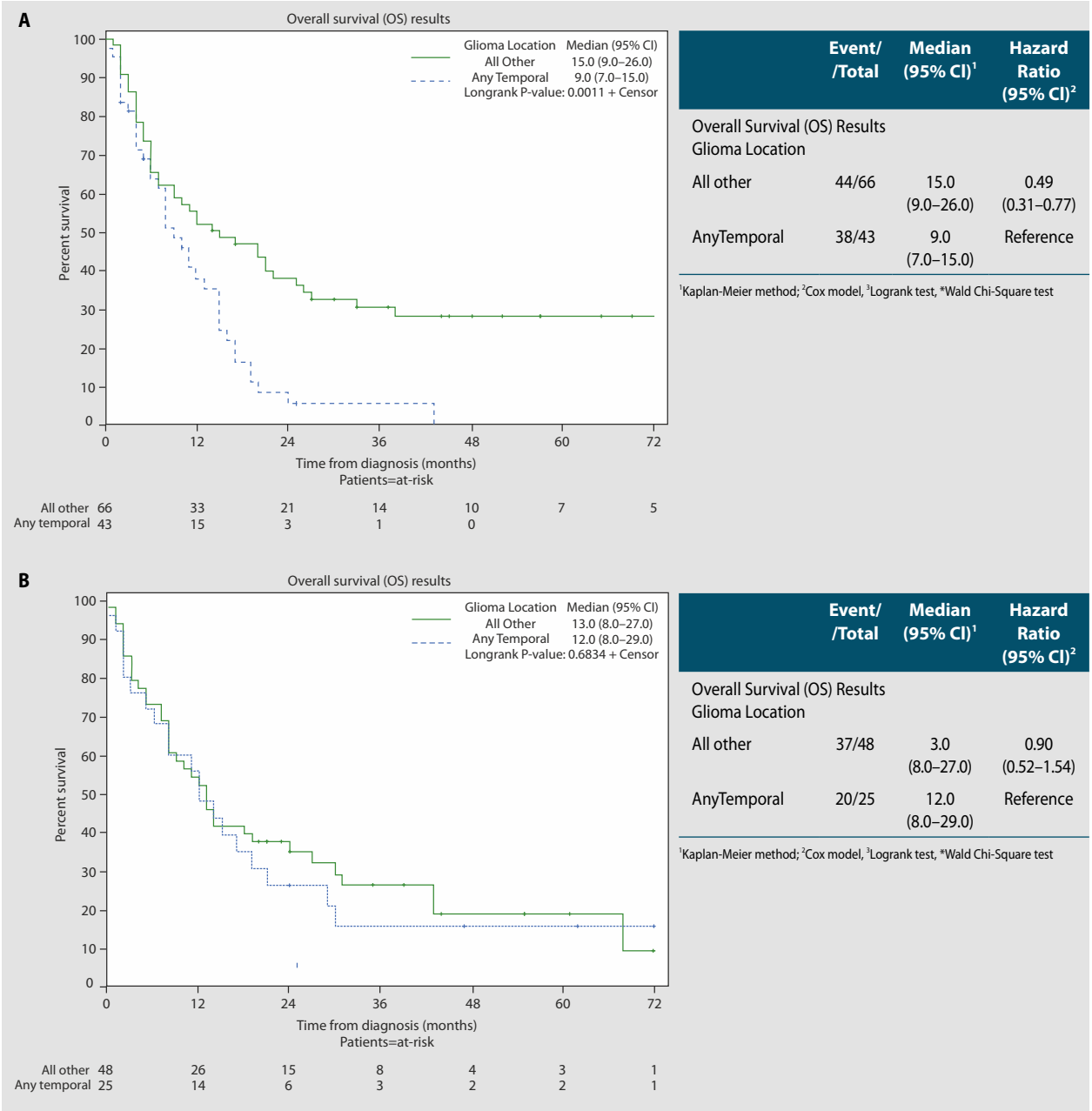
[1]Kaplan-Meier method; [2]Cox model, [3]Logrank test

Figure 2. Overall survival analysis of temporal lobe tumours *vs* all other tumours

Glioma subtypes

Overall, 112 of 182 cases were glioblastoma (61.5%), 50 cases were grade I–III astrocytoma (27.5%), nine cases were oligodendroma (4.9%), and the remaining 11 cases were unspecified glioma or gliosarcoma (6.0%). The non-glioblastoma astrocytoma cases included 37 grade III and 13 grade I–II. As expected, glioblastoma patients had significantly poorer survival than astrocytoma and other tumour types ($p < 0.0001$), however this seems to be driven by underlying differences in patient age, grade at diagnosis, and surgical approach (adjusted p-value = 0.128).

Differences were observed between the types of tumour identified at different anatomical locations. Of the 50 tumours confined to the temporal lobe, 37 of them were glioblastoma (74.0%) while five were grade III astrocytoma (10.0%), two were grade I–II astrocytoma (4.0%) and one was oligodendroma (2.0%). Of the 51 tumours confined to the frontal lobe, 28 were glioblastoma (54.9%) while 11 were grade III



	Event/ /Total	Median (95% CI)[1]	Hazard Ratio (95% CI)[2]
Overall Survival (OS) Results Glioma Location			
All other	44/66	15.0 (9.0–26.0)	0.49 (0.31–0.77)
AnyTemporal	38/43	9.0 (7.0–15.0)	Reference

[1]Kaplan-Meier method; [2]Cox model, [3]Logrank test, *Wald Chi-Square test

	Event/ /Total	Median (95% CI)[1]	Hazard Ratio (95% CI)[2]
Overall Survival (OS) Results Glioma Location			
All other	37/48	3.0 (8.0–27.0)	0.90 (0.52–1.54)
AnyTemporal	20/25	12.0 (8.0–29.0)	Reference

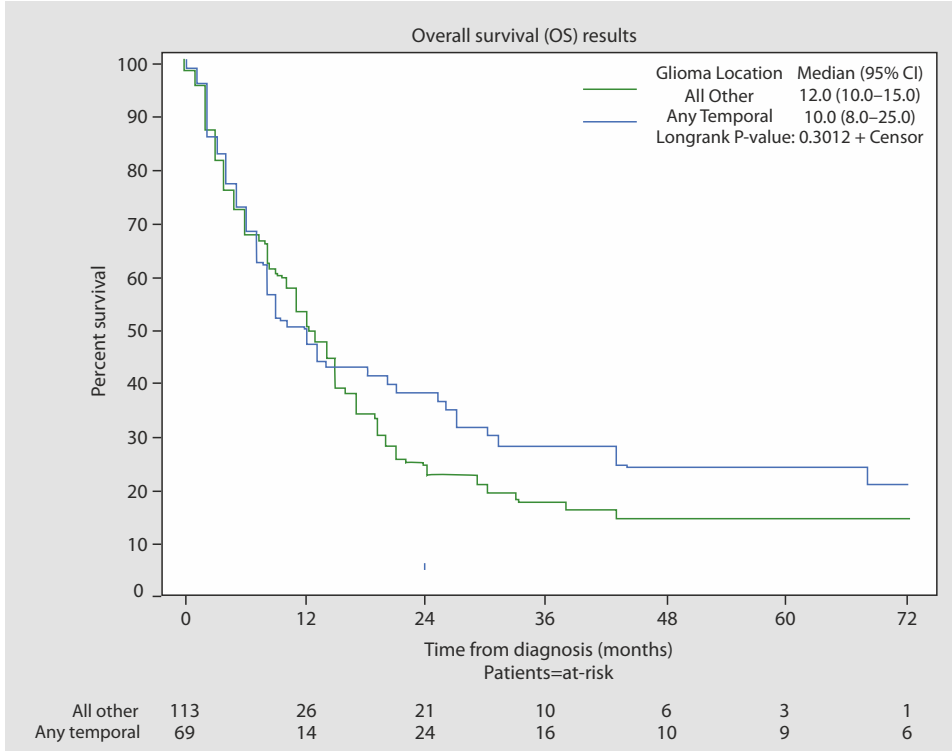
[1]Kaplan-Meier method; [2]Cox model, [3]Logrank test, *Wald Chi-Square test

Figure 3. Subgroup analysis showing survival in (**A**) male participants only and (**B**) female participants only

astrocytoma (21.2%), three were grade I–II astrocytoma (5.9%), and six were oligodendroma (11.8%).

Genetics

We collected the available data on the presence of IDH1 mutations, 1p19q deletion, ATRX presence/absence, and MGMT methylation (Tab. 3). Due to the relatively recent advent of clinical genomics, there was a limited amount of data available. IDH1 mutation/non-mutation was the most frequently reported piece of genomic data, with 82 cases (45.1%) having this information available. Of these 82, 72 cases (87.8%) were IDH1 non-mutated and the other 10 (12.2%) were mutated (Tab. 4). Six of the 10 reported IDH1 mutations were found in frontal lobe tumours, with the other four spread across temporal, thalamic, and other tumours. The 72 reported IDH-1 non-mutated tumours were located in the following regions: 20 temporal lobe (27.8%), 18 frontal lobe (25.0%), nine parietal lobe (12.5%), four occipital lobe (5.5%), two thalamic (2.8%), and 19 multifocal/other (26.4%). The presence of IDH-1 mutation conferred a statistically significant overall survival benefit (HR = 0.18, p = 0.007). This mutation was present in 4% of our temporal lobe cases, compared to 12% of our frontal lobe cases.



	Event/ /Total	Median (95% CI)[1]	Hazard Ratio (95% CI)[2]	Survival Estimates (95% CI)[1]	P-value
Overall Survival (OS) Results					
Glioma Location					0.3012[3]
All Other	87/113	12.0 (10.0–15.0)	1.20 (0.84–1.69)	12 Months: 49.1 (40.5–59.6%) 24 Months: 21.9 (15.1–31.7%) 36 Months: 17.4 (11.0–27.4%) 60 Months: 13.9 (8.0–24.1%)	
Any Frontal	52/69	10.0 (8.0–25.0)	Reference	12 Months: 46.8 (36.3–60.4%) 24 Months: 37.6 (27.6–51.2%) 36 Months: 27.8 (18.7–41.2%) 60 Months: 23.8 (15.2–37.3%)	

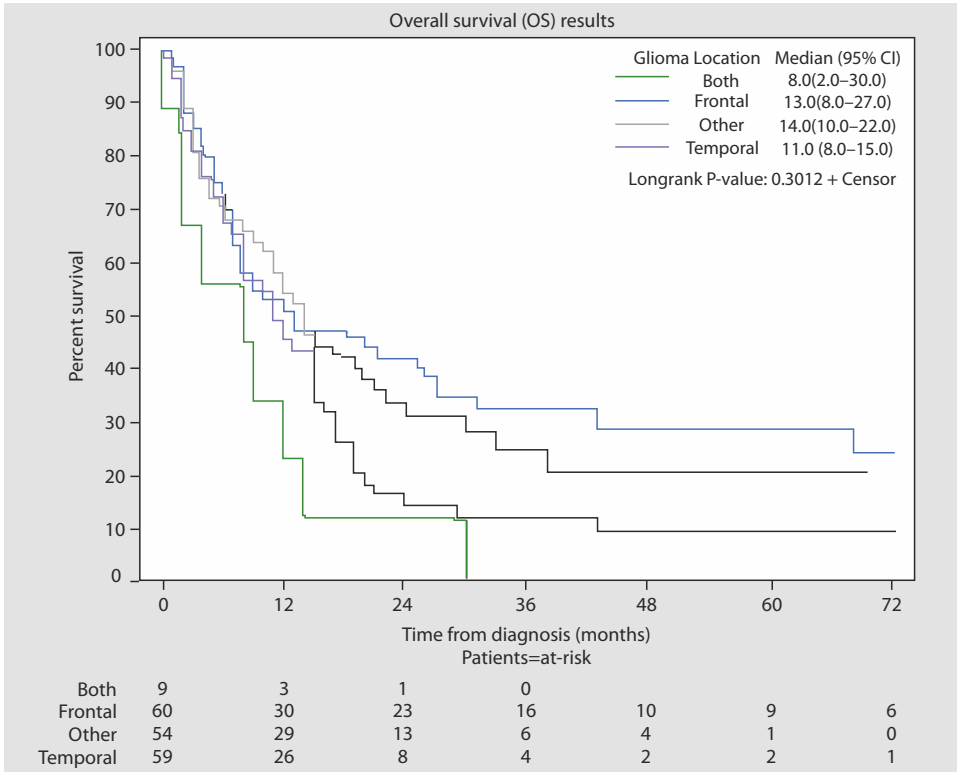
[1]Kaplan-Meier method; [2]Cox model, [3]Logrank test

Figure 4. Overall survival analysis of frontal lobe tumours *vs* all other tumours

1p19q results were reported for 21 of our 182 patients. 12 of these 21 patients had the 1p19q deletion, and nine of those deletions were found in tumours confined to the frontal lobe. ATRX presence was tested in 42 of our 182 cases. ATRX was present in 40 of these 42 cases. Finally, MGMT methylation was tested in 47 of the 182 cases, with 22 cases showing methylation, 23 cases lacking methylation, and two cases showing indeterminate results. Due to small sample sizes, statistical tests were not conducted for 1p19q, ATRX, or MGMT results.

Discussion

This study analysed 182 tissue-proven glioma cases seen at our institution over a 10-year period. In general, tumours were more likely to be found in the right brain (51.1%) compared to the left (40.1%). This replicates findings from a previous epidemiologic study [8]. Two thirds of these gliomas (66.5%) involved the frontal lobe, the temporal lobe, or both. The remaining tumours were spread among the other lobes of



	Event/ /Total	Median (95% CI)[1]	Hazard Ratio (95% CI)[2]	Survival Estimates (95% CI)[1]	P-value
Overall Survival (OS) Results					
Glioma Location					0.0195*
Both	9/9	8.0 (2.0–30.0)	1.59 (0.78–3.24)	12 Months: 22.2 (6.5–75.4%) 24 Months: 11.1 (1.8–70.5%) 36 Months: 0.0 (0.0–0.0%) 60 Months: 0.0 (0.0–0.0%)	
Frontal	43/60	13.0 (8.0–27.0)	0.63 (0.42–0.96)	12 Months: 50.6 (39.3–65.2%) 24 Months: 41.7 (30.7–56.6%) 36 Months: 32.2 (22.0–47.1%) 60 Months: 27.6 (17.8–42.7%)	
Other	38/54	14.0 (10.0–22.0)	0.72 (0.47–1.10)	12 Months: 53.7 (41.6–69.2%) 24 Months: 30.5 (192–462%) 36 Months: 24.0 (13.9–41.3%) 60 Months: 20.0 (10.4–38.3%)	

[1]Kaplan-Meier method; [2]Cox model, [3]Logrank test

Figure 5. Analysis of overall survival by location (temporal *vs* frontal *vs* both *vs* neither/other)

Table 2. Surgical treatment modality by glioma location

Location	Total gross resection	Subtotal/partial resection	Excisional biopsy	Total
Brainstem	0 (0.0%)	1 (33.3%)	2 (66.7%)	3
Frontal	16 (31.4%)	10 (19.6%)	25 (49.0%)	51
Frontoparietal	2 (22.2%)	1 (11.1%)	6 (66.7%)	9
Frontotemporal	0 (0.0%)	0 (0.0%)	7 (100.0%)	7
Occipital	3 (42.9%)	1 (14.2%)	3 (42.9%)	7
Other*	1 (25.0%)	1 (25.0%)	2 (50.0%)	4
Multifocal	0 (0.0%)	1 (9.1%)	10 (90.9%)	11
Parietal	7 (31.8%)	5 (22.7%)	10 (45.5%)	22
Temporal	17 (34.0%)	11 (22.0%)	22 (44.0%)	50
Temporal, Frontal, Corpus Callosum	0 (0.0%)	0 (0.0%)	2 (100.0%)	2
Temporal, Parietal, Occipital	2 (100.0%)	0 (0.0%)	0 (0.0%)	2
Temporoparietal	3 (42.8%)	2 (28.6%)	2 (28.6%)	7
Thalamus	0 (0.0%)	0 (0.0%)	7 (100.0%)	7
Total	51 (28.0%)	33 (18.1%)	98 (53.9%)	182

*Four cases marked 'other' were: parietooccipital, cerebellum, intraventricular, and corpus callosum

Table 3. Glioma molecular characteristics

	Astrocytoma grades I -II (N = 13)	Astrocytoma grade III (N = 37)	Glioblastoma (N = 112)	Other (N = 20)	Total (N = 182)
IDHI					
Mutated	1 (20.0%)	3 (15.0%)	1 (2.0%)	5 (62.5%)	10 (12.2%)
Non-mutated	4 (80.0%)	17 (85.0%)	48 (98.0%)	3 (37.5%)	72 (87.8%)
Not tested	8	17	63	12	100
1p19Q					
Deleted	0 (0.0%)	2 (50.0%)	1 (20.0%)	9 (81.8%)	12 (57.1%)
Non-deleted	1 (100.0%)	2 (50.0%)	4 (80.0%)	2 (18.2%)	9 (42.9%)
Not tested	12	33	107	9	161
ATRX					
Present	4 (100.0%)	8 (88.9%)	25 (92.6%)	3 (100.0%)	40 (93.0%)
Absent	0 (0.0%)	0	2 (7.4%)	0 (0.0%)	2 (4.7%)
Indeterminate	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)	1 (2.3%)
Not tested	9	28	85	17	139
MGMT					
Methylated	0 (0.0%)	1 (25.0%)	21 (51.2%)	0 (0.0%)	22 (46.8%)
Un-methylated	1 (100.0%)	3 (75.0%)	18 (43.9%)	1 (100.0%)	23 (48.9%)
Indeterminate	0 (0.0%)	0 (0.0%)	2 (4.9%)	0 (0.0%)	2 (4.3%)
Not tested	12	33	71	19	135

the brain, the thalamus, and the brainstem. Survival analysis showed the poorest overall survival in gliomas affecting the temporal lobe. Tumours affecting the temporal lobe were more likely to be WHO grade 4/glioblastomas, less likely to have IDH-1 mutations, and were associated with higher mean and median age at diagnosis. Patients with temporal lobe tumours and patients with frontal lobe tumours were equally likely to undergo resective surgery, so differences in treatment modality alone do not explain the difference in survival. Interestingly, subgroup analysis revealed the association between temporal location and poorer survival to be true only in males, both before and after adjustment for grade, age, and surgical resection. Based on this data we can conclude that in this data set, patients with temporal lobe gliomas had poorer overall survival than patients with frontal (and other location) gliomas. This finding appears to be driven by the molecular and clinical characteristics of these tumours and patients.

Table 4. Frequency of IDH-1 mutation by tumour type

	IDH-1 mutation frequency		
	Mutated	Non-mutated	Total
Glioblastoma	1 (2.0%)	48 (98.0%)	49 (59.7%)
Astrocytoma	4 (16.0%)	21 (84.0%)	25 (30.5%)
Other	5 (62.5%)	3 (37.5%)	8 (9.8%)
Total	10 (12.2%)	2 (87.8%)	82 (100%)

The results of our study provide further evidence for the hypothesis that gliomas preferentially arise in particular neuroanatomical locations, and that these locations have implications for clinical outcomes.

Our finding that the frontal and temporal lobes are the most common primary sites of gliomas replicates previous analyses of glioma by lobe of the brain [2, 8]. It is also of interest that the three most frequent locations for gliomas were associated with frontal, temporal, and parietal lobes (37.8%, 37.3%, 21.9% respectively), but not with occipital lobe (total of 4.9%). This distribution is not attributable to differences in volumes (and hence differences in the simple probability of glioma occurrence) among these structures. While human occipital lobe volume equals approximately only half of the volume of frontal lobe, the frequencies of glioma incidents in these two structures differ by a factor of 7.7, as indicated by our data. Furthermore, the negligible difference in the volume of parietal and occipital lobes cannot account for the 7.6-fold difference in glioma frequency between these two lobes [8, 10]. At the same time, the seemingly smaller incidence of gliomas in parietal lobes is actually higher than the incidence in frontal lobes when corrected for the volumes of the structures.

A plausible explanation for this observed variation in glioma frequencies might lie with the anatomical distribution of neuronal stem cell (NSC) population in the mammalian brain. The population of these cells is present and is proliferative in the brain throughout the lifespan of an individual [11, 12]. Also, NSCs are believed to be a source of so-called 'brain cancer stem cells' — cells that may give rise to gliomas [13–15]. Importantly, the largest migratory population of NSCs is found in the sub-ventricular zone (SVZ) in the wall of lateral ventricles [11, 12]. Lateral ventricles penetrate frontal, temporal and parietal lobes extensively, but the impinging of occipital lobe by posterior horn of lateral ventricle is limited. Further, in a rodent model, it has been demonstrated that there is a gradient of NSCs density and proliferative potential along the ventricular neuroaxis, with lower values found at the posterior (occipital) horn of lateral ventricles [16]. Thus, the differences in glioma frequencies among cortical lobes could be – at least partially – attributed to the degree of proximity between each lobe and active neuronal stem cell population. Such an interpretation is also consistent with the likely role of NSCs as a cell population where brain cancer stem cells originate.

Our study found that tumours involving the temporal lobe are associated with poorer survival than other tumours, specifically in males. Previous reports on this association are contradictory, with one analysis similarly reporting poorer prognosis in temporal lobe gliomas and another study reporting improved survival in these patients [2]. This may be attributable to differences in patient demographics. Our study and the prior study that found poorer survival in temporal lobe patients were both conducted in the western United States, while the study that reported improved survival in these patients was conducted in Finland. Sufficient genetic and other clinical data is not available to determine to what extent this difference is attributable to variations in patient populations [9]. The gender differences in glioma outcomes are supported by previously published neuro-oncology and basic physiology research [17–19].

Our intention to analyse the molecular characteristics of these tumours was limited by the relatively recent prevalence of clinical genomic testing. We reviewed patient records from 2008-2018, and less than 50% of cases had genetic data available. While these tests have become a standard of care for most cancer patients, this was not the case in the 2000s. Given the decreasing cost and increasing availability of genomic assays, and the emerging importance of genomic information in clinical care, it is increasingly important that neuro-oncologists strive to collect this information from as many of their patients as possible. As access to this data becomes more prevalent, researchers will become better equipped to re-visit the hypothesis that molecular characteristics drive differences in tumour incidence and outcome in different regions of the brain. Our study did find that prognostically favourable IDH-1 mutations were three times less likely in temporal lobe tumours compared to frontal lobe tumours [20]. Unfortunately, due to small sample sizes we were unable to conduct statistical analyses of this observation.

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References

1. Pignatti F, van den Bent M, Curran D, et al. European Organization for Research and Treatment of Cancer Brain Tumor Cooperative Group, European Organization for Research and Treatment of Cancer Ra-

diotherapy Cooperative Group. Prognostic factors for survival in adult patients with cerebral low-grade glioma. J Clin Oncol. 2002; 20(8): 2076–2084, doi: 10.1200/JCO.2002.08.121, indexed in Pubmed: 11956268.
2. Simpson JR, Horton J, Scott C, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive Radiation Therapy Oncology Group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys. 1993; 26(2): 239–244, doi: 10.1016/0360-3016(93)90203-8, indexed in Pubmed: 8387988.
3. Marchel ANAARATDATCAPKAEMAA. Predictors of Class I epilepsy surgery outcome in tumour-related chronic temporal lobe epilepsy in adults. : Vol 532019.
4. Ładziński KMABB-BAAHAPAAHMAP. Surgical treatment of adult patients with thalamic tumors with the aid of tractography, fMRI, transcranial electrical stimulation and direct electrical stimulation of the subcortical white matter. : Vol 522018.
5. Mandonnet E, Capelle L, Duffau H, et al. Preferential brain locations of low-grade gliomas. Cancer. 2004; 100(12): 2622–2626, doi: 10.1002/cncr.20297, indexed in Pubmed: 15197805.
6. Jakola AS, Unsgård G, Myrmel KS, et al. Low grade gliomas in eloquent locations - implications for surgical strategy, survival and long term quality of life. PLoS One. 2012; 7(12): e51450, doi: 10.1371/journal.pone.0051450, indexed in Pubmed: 23251537.
7. Tang Q, Lian Y, Yu J, et al. Anatomic mapping of molecular subtypes in diffuse glioma. BMC Neurol. 2017; 17(1): 183, doi: 10.1186/s12883-017-0961-8, indexed in Pubmed: 28915860.
8. Larjavaara S, Mäntylä R, Salminen T, et al. Incidence of gliomas by anatomic location. Neuro Oncol. 2007; 9(3): 319–325, doi: 10.1215/15228517-2007-016, indexed in Pubmed: 17522333.
9. Nizamutdinov D, Stock EM, Dandashi JA, et al. Prognostication of Survival Outcomes in Patients Diagnosed with Glioblastoma. World Neurosurg. 2018; 109: e67–e74, doi: 10.1016/j.wneu.2017.09.104, indexed in Pubmed: 28951270.
10. Kennedy DN, Lange N, Makris N, et al. Gyri of the human neocortex: an MRI-based analysis of volume and variance. Cereb Cortex. 1998; 8(4): 372–384, doi: 10.1093/cercor/8.4.372, indexed in Pubmed: 9651132.
11. Lim DA, Alvarez-Buylla A. The Adult Ventricular-Subventricular Zone (V-SVZ) and Olfactory Bulb (OB) Neurogenesis. Cold Spring Harb Perspect Biol. 2016; 8(5), doi: 10.1101/cshperspect.a018820, indexed in Pubmed: 27048191.
12. Quiñones-Hinojosa A, Sanai N, Gonzalez-Perez O, et al. The human brain subventricular zone: stem cells in this niche and its organization. Neurosurg Clin N Am. 2007; 18(1): 15–20, vii, doi: 10.1016/j.nec.2006.10.013, indexed in Pubmed: 17244550.
13. Capdevila C, Rodríguez Vázquez L, Martí J. Glioblastoma Multiforme and Adult Neurogenesis in the Ventricular-Subventricular Zone: A Review. J Cell Physiol. 2017; 232(7): 1596–1601, doi: 10.1002/jcp.25502, indexed in Pubmed: 27458813.
14. Sanai N, Alvarez-Buylla A, Berger MS. Neural stem cells and the origin of gliomas. N Engl J Med. 2005; 353(8): 811–822, doi: 10.1056/NEJMra043666, indexed in Pubmed: 16120861.
15. Singh S, Dirks PB. Brain tumor stem cells: identification and concepts. Neurosurg Clin N Am. 2007; 18(1): 31–8, viii, doi: 10.1016/j.nec.2006.10.014, indexed in Pubmed: 17244552.
16. Golmohammadi MG, Blackmore DG, Large B, et al. Comparative analysis of the frequency and distribution of stem and progenitor cells in the adult mouse brain. Stem Cells. 2008; 26(4): 979–987, doi: 10.1634/stemcells.2007-0919, indexed in Pubmed: 18203672.
17. Gittleman H, Ostrom QT, Stetson LC, et al. Females have the survival advantage in glioblastoma. Neuro Oncol. 2018; 20(4): 576–577, doi: 10.1093/neuonc/noy002, indexed in Pubmed: 29474647.
18. Rubin JB, Lagas JS, Broestl L, et al. Sex differences in cancer mechanisms. Biol Sex Differ. 2020; 11(1): 17, doi: 10.1186/s13293-020-00291-x, indexed in Pubmed: 32295632.
19. Yang W, Warrington NM, Taylor SJ, et al. Sex differences in GBM revealed by analysis of patient imaging, transcriptome, and survival data. Sci Transl Med. 2019; 11(473), doi: 10.1126/scitranslmed.aao5253, indexed in Pubmed: 30602536.
20. Cohen AL, Holmen SL, Colman H. IDH1 and IDH2 mutations in gliomas. Curr Neurol Neurosci Rep. 2013; 13(5): 345, doi: 10.1007/s11910-013-0345-4, indexed in Pubmed: 23532369.