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Outlining the Molecular Profile of Glioblastoma: Exploring the Influence of Subventricular Zone Proximity

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ABSTRACT

AIM: To investigate the correlation between specific glioblastoma multiforme (GBM) molecular markers and their proximity to the subventricular zone (SVZ) to uncover potential prognostic indicators and therapeutic strategies.

MATERIAL and METHODS: The study retrospectively analyzed 171 patients who underwent surgery for supratentorial GBM from 2016 to 2022. GBMs were categorized into SVZ contact (SVZ + GBM) and SVZ noncontact (SVZ-GBM) groups. We analyzed molecular markers, such as IDH1, P53, ATRX, Ki67, GFAP, and Olig2.

RESULTS: SVZ + GBM tumors were larger (12.2 cm3) than SVZ-GBM tumors (4.8 cm^3; $p<0.001$). Additionally, IDH1 mutation was negative in 100% of SVZ-GBM tumors; ATRX loss was more prevalent in SVZ + GBM tumors (34.3%) than in SVZ-GBM tumors (4.5%; $p<0.001$). There was no correlation between SVZ contact and the p53 value ($p=0.134$). Furthermore, no difference was observed in the association of the Ki67 proliferation index and Olig2 positivity with SVZ contact ($p=0.306$, $p=0.071$, respectively). However, there was a correlation between IDH1 mutation and SVZ contact, with all IDH1-positive tumors showing SVZ contact ($p=0.009$).

CONCLUSION: This study revealed a correlation between SVZ contact in GBM and specific molecular markers, specifically IDH1 mutation, ATRX loss, and tumor size. SVZ contact could serve as criterion for categorizing GBMs, thus contributing to an improved understanding of the disease and potential therapeutic interventions.

KEYWORDS: Subventricular zone, Glioblastoma multiforme, Isocitrate dehydrogenase, Neural stem cells, Glioblastoma-initiating cells

ABBREVIATIONS: GBM: Glioblastoma multiforme, **SVZ:** Subventricular zone, **SVZ + GBM:** Subventricular Zone-contact glioblastoma multiforme, **SVZ-GB:** Subventricular zone noncontact glioblastoma multiforme, **IDH1:** Isocitrate dehydrogenase, **ATRX:** Alpha thalassemia/mental retardation syndrome X-linked, **Ki67:** Marker of proliferation Ki-67, **GFAP:** Glial fibrillary acidic protein, **Olig2:** Oligodendrocyte transcription factor 2

INTRODUCTION

Glioblastoma multiforme (GBM), the most common and aggressive glial tumor in adults, originates from glial or precursor cells within the central nervous system (17,20). Accounting for over 50% of all malignant glioma cases, it has significant morbidity and mortality rates (12). Conventional therapy involves surgical resection, followed by concurrent radiation therapy, TMZ administration, and 6–12 TMZ cycles (5). However, current treatments for GBM remain markedly inadequate, yielding a median survival of 9–15 months (9,16).

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The urgent need to understand the origins of GBM and identify therapeutic targets has sparked a comprehensive exploration of its prognostic factors and molecular profile (2,3). Emerging evidence supports the role of several markers, including isocitrate dehydrogenase (IDH), p53 mutation, ATRX loss, ki67 proliferation index, GFAP, and Olig positivity, in predicting prognosis and shaping the tumor's molecular identity (18,23). The role of the subventricular zone's (SVZ), a 4-mm thick embryonic layer bordering the lateral ventricles, is particularly intriguing (13). As primary neural and glial cell production site housing neural stem/progenitor cells (NSCs), the SVZ is integral to brain development (6). Molecular analyses underscored the overlapping surface protein profile of SVZ NSCs and glioblastoma-initiating cells, providing substantial support for two GBM genesis theories: stem cell and astrocyte differentiation (1,11). Further, clinical studies indicate the capacity of SVZ-located NSCs for oncogenic transformation, possibly leading to GBM formation (1).

This study aimed to elucidate the relationship between GBM molecular markers and SVZ-contacting GBMs and to extrapolate molecular prognostic information from radiological data. A secondary aim was to explore correlations between SVZ distance and time until the second surgery in patients with GBM.

MATERIAL and METHODS

Study Population

This study adheres to the ethical principles stipulated in the Declaration of Helsinki of the World Medical Association with approval from the Istanbul Medipol University Clinical Research Ethics Committee numbered 1016/2023. Our sample comprised patients who underwent surgical intervention for supratentorial GBM at our neurosurgery clinic between January 1, 2016, and May 12, 2022. The analysis was based on complete pathological specimens procured during the surgeries. We divided patients into two categories according to the GBM tumor location: tumors contacting the SVZ (SVZ + GBM) and or devoid of such contact (SVZ-GBM).

Our study only included patients whose records were accessible via hospital archives or telephonic communication. Each patient had undergone the standard GBM treatment regimen comprising surgery, chemotherapy, and radiotherapy. In addition, we considered individuals who had to undergo a second surgical procedure within six months of the first one. However, the study did not perform a molecular analysis from the 2nd operation. As the pathological samples were procured before the 2021 WHO classification, our study included glioblastomas with IDH mutations. These tumors were not classified as IDH-mutated astrocytomas.

Imaging of the Tumor

The precise location of a tumor before surgical intervention was determined using either computed tomography or magnetic resonance imaging (MRI). All MRI images were obtained using either 1.5 T or 3-T systems (Siemens, Erlangen, Germany). The tumor size was calculated based on its maximum diameter, as observed in preoperative images. The interaction between the contrast-enhancing portion of the tumor and SVZ was evaluated using preoperative MRI. The tumor's distance from the SVZ was defined as the minimal distance between the SVZ and the tumor, measured directly from preoperative images (Figure 1). The nearest tumor component was the point from which the SVZ distance was measured. The preoperative tumor volume was computed using the ellipsoid volume formula: V. (4/3) Pi (a/2) (b/2) (c/2) (11).

Surgical Procedures

Based on the operational notes and postoperative imaging findings, the procedures were categorized into subtotal and gross total resection. If no residual contrast enhancement was observed in the postoperative images, it was classified as a gross total resection (GTR). Conversely, in case of enhancement, it was considered a subtotal resection (STR). Our study excluded patients with recurrent GBMs, those who had previously undergone surgery or received prior chemotherapy and radiotherapy, and those with varying tumor pathologies who underwent surgical procedures. Patients who declined surgical intervention, radiation therapy, or chemotherapy were excluded from the study as well.

Molecular Analysis

Patient demographic data (sex, age) were retrieved from the electronic hospital and national databases. A single experienced neuropathologist evaluated the pathological specimens from the fully extracted tumor. The tumor samples were examined for the presence of IDH1 mutation, tumor protein (P53) loss, ATRX loss, Ki67, GFAP, and Olig2. If a secondary operation was performed, the time elapsed from the initial procedure was recorded as well.

Statistical Analysis

Data analysis was conducted using SPSS-v15 for Microsoft Windows. For categorical variables, descriptive statistics were used to understand the data structure. The primary statistical approach was to count the number of occurrences of each category and to calculate the percentage of each type in the total dataset. Conversely, numerical variables were analyzed by computing the mean, standard deviation, and median. We used the Chi-Square test to investigate differences between groups in categorical data. The numerical data in our study were not normally distributed; therefore, we used the Mann–Whitney U test. To investigate the relationship between numerical variables, we employed Spearman's correlation analysis. In addition, we used receiver operating characteristic curve analysis to determine the cut-off value. Our accepted level of significance, or the "alpha," was 0.05.

RESULTS

Demographic Data

The study comprehensively analyzed demographic and clinical characteristics of 171 patients diagnosed with GBM (Table I). The patient group was nearly balanced in sex, with females accounting for 45.6% and males for the rest. The

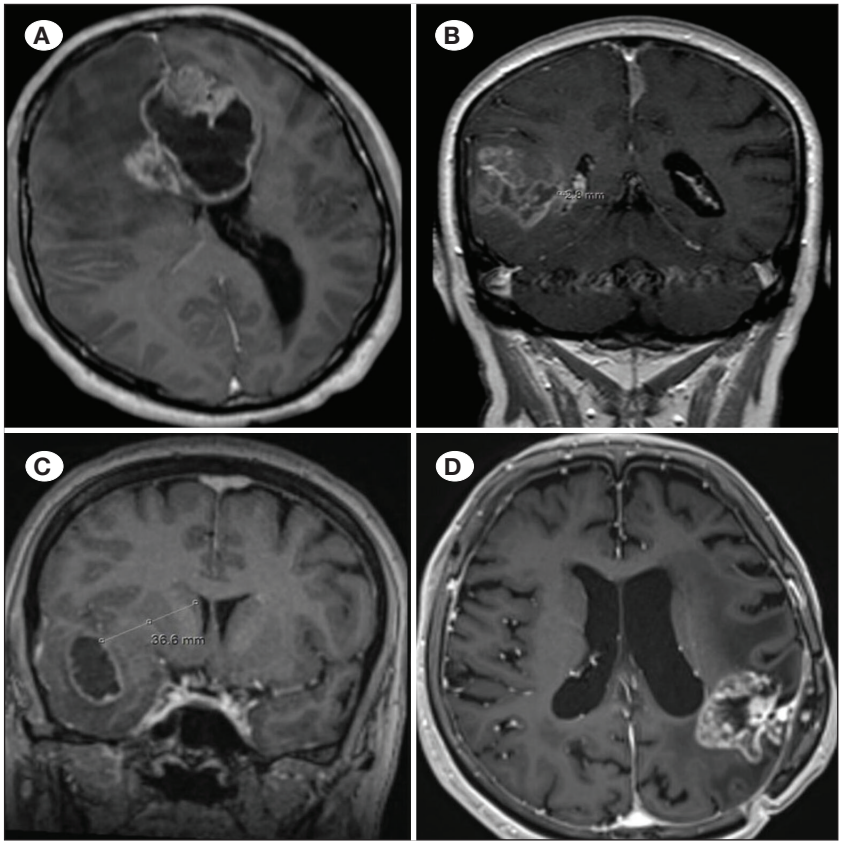

Figure 1: Magnetic resonance images for several glioblastoma cases according to the distance from the subventricular zone. **A)** Tumor invasive to the SVZ **B)** Tumor at a distance of 2.8 mm from the SVZ **C)** Tumor at a distance of 36.6 mm from the SVZ **D)** Tumor in contact with the SVZ.

Table I: Distribution of the General Demographic Characteristics of the Cases

Variables	Frequency	p-value
Gender, n (%)	Female: 78 (45.6); Male: 93 (54.4)	0.508
Age, year	55.3 ± 14.3 (12-87)	
Side, n (%)	Left: 75 (43.9); Right: 96 (56.1)	0.354
Localization, n (%)	Frontal: 30 (17.5); Frontoparietal: 6 (3.5); Frontotemporal: 3 (1.8); Occipital: 12 (7.0); Occipitotemporal: 6 (3.5); Parietal: 57 (33.3); Parietooccipital: 15 (8.8); Parietotemporal: 6 (3.5); Temporal: 33 (19.3) *; Thalamus: 3 (1.8)	**<0.001**
Size, year	9.33 ± 6.72 (0,5-40,6)	
SVZ contact, n (%)	No: 66 (38.6); Yes: 105 (61.4)	0.085
SVZ distance, mm	6.47 ± 9.69 (0-32)	
Operation Border, n (%)	Gross total: 99 (57.9); Subtotal: 72 (42.1)	0.233
IDH_1, n (%)	Negative: 144 (84.2) *; Positive: 27 (15.8)	**<0.001**
P_{53}, n (%)	Negative: 24 (14.0); Positive: 147 (86) *	**<0.001**
ATRX loss, n (%)	No: 132 (77.2) *; Yes: 39 (22.8)	**<0.001**
Ki_{67}	29.5 ± 15.9 (10-85)	
$GFAP/Olig_2$	Positive/Negative: 141 (82.5) *; Positive/Positive: 30 (17.5)	**<0.001**
2nd Operation, n (%)	No: 117 (68.4) *; Yes: 54 (31.6)	**0.005**

SVZ contact: *Whether the tumor or lesion has contact with the subventricular zone;* ***SVZ distance:*** *The distance of the tumor or lesion from the subventricular zone;* ***Operation Border:*** *The extent of the surgical removal of the tumor; Gross total indicates the entire tumor was removed; subtotal indicates part of the tumor was removed.* ***IDH1, P53, ATRX loss, GFAP/Olig2:*** *These are specific genetic markers or proteins that can be negative (not detected) or positive (detected) in the tumor tissue.* ***Ki67(%):*** *Ki-67 is a protein that is used as a marker of cell proliferation. "Mean±SD and "Min-Max" were used for Age, Size, and SVZ distance.*

age of the participants ranged from 12 to 87 years old, with an average age of 55.3 years. When considering the brain hemisphere where the tumors were located, were similarly distributed 43.9% in the left hemisphere and 56.1% in the right hemisphere. In terms of localization, tumors were predominantly parietal (33.3%), temporal (19.3%), and frontal (17.5%). A significant variance was noticed in tumor localization (p<0.001). Tumor volumes ranged from 0.5 to 40 cm^3, with an average volume of 9.33 cm^3.

When assessing contact with SVZ, 61.4% of the tumors were in contact, whereas 38.6% were not. The average distance to the SVZ was 6.47 (range 0 –32) mm. Approximately 57.9% of the tumors were treated with GTR, and STR was performed for the remaining 42.1%. Molecular characteristics of the tumors indicated 84.2% were IDH1-negative. A significant 86.3% were p53 positive, but only 77.2% had an ATRX deletion. Olig2 was negative in 82.5% of the samples. The ki67 proliferation index, a measure of active cell division, ranged from 10 to 85, with an average of 29.5. Finally, a second procedure within the first six months was required for only 31.6% of the patients.

Table II compares SVZ + GBM with SVZ-GBM groups. While the operating margin was similar (p=0.212), a remarkable difference was observed in the mean tumor size, being larger for SVZ + GBM (12.2 cm^3) than for SVZ-GBM (4.8 cm^3; p<0.001). Interestingly, all SVZ-GBM tumors were IDH1 mutation-negative. No significant relationship was found between SVZ contact and p53 status (p=0.134). ATRX loss was relatively rare in SVZ-GBM (only 4.5% showed ATRX loss) compared with SVZ + GBM (34.3% had ATRX loss), demonstrating a significant correlation (p<0.001). In contrast, no discernable association was found between the ki67 proliferation index, Olig2 positivity, and SVZ contact (p=0.306, p=0.071).

No significant correlation was detected between reoperation and SVZ distance (p=0.791). Table III juxtaposes patients who underwent reoperation with those who did not. The study could not find any significant difference between groups regarding tumor molecular characteristics or SVZ contact. Finally, Table IV compares the molecular features of GBMs with IDH1 mutation and their relationship with SVZ. Most IDH1-wild-type tumors (87.5%) did not show ATRX loss, whereas a most IDH1-mut tumors (77.7%) demonstrated ATRX loss (p<0.001). No significant relationship was found between IDH1 status and Olig2 (p=0.184). However, an intriguing pattern emerged where 100% of IDH1-mut tumors had SVZ contact, in contrast with 54.2% of IDH1-wild-type tumors, indicating a strong correlation between IDH1 status and SVZ contact (p=0.009).

DISCUSSION

Glioblastomas are a primary health concern because they are the most common and lethal primary central nervous system tumors. Their heterogeneity, involving diverse molecular and genetic characteristics, has sparked many investigations attempting to decipher their biology. Despite surgical intervention and conventional treatment, the unfavorable prognosis underscores the urgent need to develop innovative therapeutic approaches. The current study adds to our understanding of GBMs by scrutinizing their relationship with SVZ and exploring their molecular attributes.

Table II: Comparison of Tumors in Contact with and without SVZ Contact

Variables		contact		p-value
		(-)	(+)	
Size		4.8 ± 3.5 0.5-14.1 (4.1)	12.2 ± 6.8 2.5-40.6 (11.6)	**<0.001**
Operation Border	Gross total	45 (68.2)	54 (51.4)	0.212
	Subtotal	21 (31.8)	51 (48.6)	
IDH1	Negative	66 (100)	78 (74.3)	**0.009**
	Positive	0	27 (25.7)	
P53	Negative	3 (4.5)	21 (20)	0.134
	Positive	263 (95.5)	84 (80)	
ATRX loss	No	63 (95.5)	69 (65.7)	**0.009**
	Yes	3 (4.5)	36 (34.3)	
Ki67		27.3 ± 15 15-80 (25)	30.9 ± 16.6 10-85 (25)	0.306
GFAP/Olig2	Positive/Negative	63 (95.5)	78 (74.3)	0.071
	Positive/Positive	3 (4.5)	27 (25.7)	

"No contact" and "Yes": *These columns differentiate between two study groups - those with no contact and those with contact. Specific numbers and percentages in parentheses indicate the number and proportion of individuals in each group for each variable.* ***"Mean ± SD (Min-Max)":*** *This format indicates the mean or average value plus or minus the standard deviation, as well as the minimum and maximum values in the dataset. This has been used for Size and Ki67.*

Table III: Comparison of the Characteristics of Those Who Underwent Reoperation and did not

Variables		Reoperation		p-value
		(-)	(+)	
IDH_1	Negative	102 (87.2)	42 (77.8)	0.442
	Positive	15 (12.8)	12 (22.2)	
P_{53}	Negative	21 (17.9)	3 (5.6)	0.414
	Positive	69 (82.1)	51 (94.4)	
ATRX loss	No	90 (76.9)	42 (77.8)	1.000
	Yes	27 (23.1)	12 (22.2)	
Ki_{67}		27.4 ± 13.2 15-80 (25)	33.9 ± 20.5 10-85 (25)	0.337
$GFAP/Olig_2$	Positive/Negative	96 (82.1)	45 (83.3)	1.000
	Positive/Positive	21 (17.9)	9 (16.7)	
SVZ contact	No	45 (38.5)	21 (38.9)	1.000
	Yes	72 (61.5)	33 (61.1)	

"No-Reop." and "Reoperated": *These columns differentiate between two study groups - those who did not undergo reoperation and those who did. Specific numbers and percentages in parentheses indicate the number and proportion of individuals in each group for each variable.* ***Mean±SD (Min-Max):*** *This format indicates the mean or average value plus or minus the standard deviation, as well as the minimum and maximum values that was used for Ki67.*

Table IV: Comparison of Molecular Characteristics of GBMs with and without IDH1 Mutation and Their Relationship with SVZ

Variables		IDH_1		p-value
		(-)	(+)	
P_{53}	Negative	15 (10.4)	9 (33.3)	0.103
	Positive	129 (89.6)	18 (66.7)	
ATRX loss	No	126 (87.5)	6 (22.2)	**<0.001**
	Yes	18 (12.5)	21 (77.8)	
$GFAP/Olig_2$	Positive/Negative	123 (85.4)	18 (66.7)	0.184
	Positive/Positive	21 (14.6)	9 (33.3)	
SVZ contact	No	66 (45.8)	0 (0)	**0.009**
	Yes	78 (54.2)	27 (100)	
SVZ distance (mm)		7.69 ± 10.1 0-32 (0)	0.00 0-0 (0)	0.519

"IDH_1 Negative" and "Positive": *These columns differentiate between two study groups - GBMs with and without IDH_1 mutation. Specific numbers and percentages in parentheses indicate the number and proportion of individuals in each group for each variable.* ***Mean±SD(Min-Max):*** *This format indicates the mean or average plus or minus the standard deviation, as well as the min and max values that was used for SVZ distance.*

Most primary GBMs, known as IDH-wild type, emerge *de novo*, whereas secondary GBMs (IDH-mutant) typically evolve from low-grade gliomas (4,15). Our research corroborated the ubiquitous presence of IDH-wild-type tumors while noting an increased prevalence of IDH-mutant tumors in high-risk regions such as the hypothalamus, midbrain, and medulla oblongata. Knowing the cell type resulting in GBMs could unlock insights into their etiology, prognosis, and potential treatment strategies (7,21). Our results support that NSCs, particularly those in the SVZ, could be the origin of IDH-wild-type GBMs. Interestingly, a significant fraction of GBMs were not in direct contact with the SVZ, suggesting the potential migration of SVZ-originating cells to distant cortical regions. Moreover, SVZ + GBM tumors were significantly larger at diagnosis, which could reflect a late manifestation of symptoms due to their deeper and remote location.

Our results also support a possible role for p53 mutations in primary GBMs distant from the SVZ (8,10,22). Lee et al. identified low-level GBM driver mutations in SVZ samples derived from tissues of IDH-wild-type SVZ-GBM patients (8). In addition, Wang et al. developed a mouse model with p53 mutations in NSCs in the SVZ and demonstrated that these mutant cells migrated to distant locations (19). A remarkable 95.5% of SVZ-GBM were p53-positive, indicating the potential contribution of p53 mutations to developing GBMs. Additionally, we observed that most IDH1-negative tumors were p53-positive, although the statistical significance of this observation was not robust enough to draw definitive conclusions. Further, our results indicated a potential association between SVZ contact and Olig2, although the statistical significance of this finding remains unclear. Moreover, ATRX loss, commonly associated with malignant progression, was more prevalent in IDH1 mutation-associated tumors than in IDH1 wild-type tumors. Intriguingly, ATRX loss was less frequent in SVZ-GBM tumors, which exhibited a more malignant progression, highlighting the potential of ATRX loss as a marker for both IDH-wild type and SVZ-distant tumors.

Some studies have suggested a poor prognostic impact of SVZ + GBM tumors, which might expedite transfer to the contralateral side (6,13,14). Our analysis revealed that a significant fraction of patients who required reoperation within the first six months had SVZ + GBM tumors. This may indicate that SVZ + GBM tumors progress more rapidly, necessitating closer follow-up and potentially earlier reoperation.

One limitation of this study is the relatively small number of patients and its retrospective design. The accuracy of the results can be compromised if past hospital records were incomplete or contain erroneous information and/or potential systematic errors. This constrains the generalizability of our findings and requires validation in a larger patient cohort. We do not know whether SVZ-GBM tumors originate from the SVZ or grow toward this region. An analysis of survival rates and treatment responses between the two GBM groups was not conducted here. Future research should focus on this point to increase our understanding of GBM prognosis and treatment efficacy. Further, a more focused analysis of the prognostic implications of IDH mutations in GBM, as per the latest WHO classification, is warranted in our future investigations.

CONCLUSION

Our findings reveal a significant association between GBMs in contact with the SVZ and IDH1, ATRX, and tumor size, but no molecular differences between GBMs based on their proximity to the SVZ. Our research highlights the influence of SVZ contact on the molecular characteristics of GBM and its potential utility for future research classification.

Declarations

Funding: The study was not supported by a foundation.

Availability of data and materials: The data supporting this study's findings are available from the corresponding author upon reasonable request.

Disclosure: The authors declare no potential conflicts of interest.

AUTHORSHIP CONTRIBUTION

Study conception and design: HSC, EU
Data collection: ES, EU
Analysis and interpretation of results: HSC, MEG
Draft manuscript preparation: ES, HSC
Critical revision of the article: EU, MEG
Other (study supervision, fundings, materials, etc...): HSC, MEG
All authors (HSC, EU, MEG, ES) reviewed the results and approved the final version of the manuscript.

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