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Ventricular Entry During Glioblastoma Resection is Associated With Reduced Survival and Increased Risk of Distant Recurrence

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BACKGROUND AND OBJECTIVES: Although subventricular zone (SVZ) involvement is known to correlate with more aggressive tumor behavior and reduced survival in glioblastoma (GBM), the role of ventricular entry (VE) on outcomes is less clear and remains debated. This study aims to investigate the impact of VE on outcomes and overall survival (OS) in GBM.

METHODS: A retrospective analysis of patients with newly diagnosed supratentorial GBMtreated between 2013 and 2023 at the University of Pittsburgh Medical Center was performed. SVZ involvement, size, and extent of resection were identified through preoperative and postoperative imaging. VE was identified through operative notes and postoperative imaging review.

RESULTS: A total of 282 patients met inclusion criteria. VE occurred in 38.3% (n = 108) of patients and was more common in those with SVZ-contacting tumors ($P < .001$). Patients who had VE had significantly lower median OS compared with non-VE (12 months vs 18 months, $P < .001$). VE was identified as an independent risk factor for decreased OS in patients with GBM, after adjusting for well-known prognostic factors and SVZ contact (hazard ratios: 1.62 [1.12-2.34], $P = .001$). Only patients who had VE developed postoperative hydrocephalus (n = 4, 1.4%, $P = .021$) and had external ventricular drain placed (n = 6, 2.1%, $P = .003$). Distant parenchymal recurrence and leptomeningeal dissemination (LMD) rates were significantly higher in the VE group compared with the non-VE group (63.9% vs 39.7%, $P < .001$, and 23.1% vs 13.2%, $P = .035$), and VE emerged as an independent predictor of distant recurrences/LMDs in multivariable logistic regression (odds ratio: 4.7 [2.11-10.4], $P < .001$).

CONCLUSION: Our data suggest that VE during GBM resection is a significant independent risk factor for decreased survival and increased distant recurrence/LMD. While maximizing tumor resection remains critical, neurosurgeons must consider the potential adverse outcomes associated with VE because it may diminish the survival benefits of gross-total resection. Prospective studies are warranted to better understand the risks and benefits of VE in GBM surgery.

KEY WORDS: Glioblastoma, Leptomeningeal disease, Periventricular, Recurrence, Subventricular zone, Ventricular entry

Glioblastoma (GBM) is the most common and aggressive malignant glial tumor in adults, characterized by its heterogeneous nature and challenging prognosis.[1,2] Despite advances in understanding its biology and improvements in surgical techniques, patient outcomes remain poor, with a median survival of 9 months without treatment and approximately 15 months with intervention.[3-5]

Emerging evidence from multiple studies suggests that GBMs in contact with the lateral ventricles are associated with poorer survival compared to noncontacting tumors.[6-12] This reduced

ABBREVIATIONS: EOR, extent of resection; **GTR,** gross-total resection; **HR,** hazard ratios; **LMD,** leptomeningeal dissemination; **NTR,** near-total resection; **OS,** overall survival; **STR,** subtotal resection; **SVZ,** subventricular zone; **VE,** ventricular entry.

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survival may be linked to the subventricular zone (SVZ), which plays a crucial role in GBM pathogenesis.[6,7,9,10,13,14] The SVZ, a neurogenic stem cell niche located along the lateral wall of the ventricles, harbors neural stem cells that may contribute to the initiation and progression of GBM in certain patients.[3,13,15,16] It has been suggested that GBM tumors in contact with the SVZ may exhibit more aggressive behavior due to the involvement of these NSCs, which are known for their resistance to conventional therapies and their role in driving tumor growth and recurrence.[3,9,13,15] Moreover, GBMs that invade the SVZ are more likely to present with multifocal disease and have a higher tendency for distant parenchymal recurrence, both of which are associated with decreased overall survival (OS).[3,6-9]

The impact of ventricular entry (VE) during the resection of GBM remains a subject of debate, with varying perspectives in the literature.[17-20] Some studies suggest that entering the ventricle during resection can lead to significant complications, potentially resulting in poorer survival.[19,20] For instance, a study by John et al[20] involving 183 cases reported significantly higher rates of complications including intraventricular hemorrhage, hydrocephalus, ventriculoperitoneal shunt or external ventricular drain placement, and infections in cases with VE. Battista et al[19] noted a significantly higher rate of leptomeningeal dissemination (LMD) in cases with VE. Moreover, Roelz et al[21] reported an association with decreased OS in VE, but only after 700 days of follow-up.

However, the literature lacks conclusive evidence supporting the negative impact of VE.[7,8,18,22] Young et al found no significant association with increased complications or reduced survival with VE after adjusting for subependymal disease, leading them to conclude that tumor location, rather than VE itself, may be the key factor associated with poorer outcomes.[7,8,18]

Our study aims to elucidate the association of VE and SVZ involvement with complications, LMD, distant recurrence, and survival in patients with GBM. By adjusting for key prognostic factors and SVZ contact, we seek to determine whether VE independently affects these outcomes and provide insights that may directly affect surgical decision-making.

METHODS

Study Design and Patient Selection

This study is approved by the Institutional Review Board and requirement for a formal patient consent was waived. The study included patients with newly diagnosed supratentorial GBM, treated at the University of Pittsburgh Medical Centerfrom January 2013 to September 2023, with follow-up until September 2024. Patients without available preoperative and postoperative imaging or follow-up data, patients whose index operation was for recurrence, those who had prior surgery/biopsy at an outside institution, and patients who underwent biopsies only were excluded.

Data Collection

Patient and tumor characteristics, operative and outcome data were collected retrospectively from electronic medical records, and managed using Research Electronic Data Capture.[23]

Two authors independently reviewed preoperative and postoperative images, and disagreements were resolved by a third author. Reviewers were blinded to patient outcomes. SVZ contact was determined whether the contrast-enhanced tumor involved the walls of the lateral ventricle or located within 2 mm of the lateral ventricular ependyma (Figure 1). Fluid-attenuated inversion-recovery signal abnormality was not considered when classifying SVZ contact because its heterogeneity may represent either edema or tumor cells. VE was assessed by identification of a breach in the ventricular wall that resulted in communication with the resection cavity on postoperative MRI (Figure 2). Extent of resection (EOR) was categorized as subtotal resection (STR), near-total resection (NTR) (<5% residual), or gross-total resection (GTR) based on tumor-specific contrast enhancement observed on postoperative MRIs, measured volumetrically.

Recurrences were classified as distant if the recurrent contrast-enhancing tumor was noncontiguous with the resection cavity or any residual tumor. The presence of LMD was evaluated through follow-up MRI assessments and was characterized by leptomeningeal contrast enhancement following the borders of the gyri and sulci or appearing as nodular enhancement within the subarachnoid space.

Statistical Analyses

Categorical variables were presented as numbers and percentages, while continuous variables were presented as median [IQR]. Comparative analyses were conducted using the *t*-test for continuous variables and the χ^2 or Fisher exact test for categorical variables, as appropriate.

OS was defined as the time from surgery to death or the last follow-up. Progression-free survival (PFS) was defined as the time from surgery to disease progression or recurrence. Disease progression and/or recurrence was defined only after a multidisciplinary assessment by a team of neurosurgeons, neuro-oncologists, neuroradiologists, and radiation oncologists, who evaluated both imaging findings and the clinical course. In addition, where applicable, advanced imaging modalities such as perfusion MRI and MR spectroscopy were used to support this determination. Kaplan-Meier curves were constructed to estimate median OS and PFS, with comparisons between groups made using the log-rank test. A multivariable Cox proportional hazards model was used to investigate the impact of VE on survival, accounting for the influence of established prognostic factors in GBM. In this analysis, covariates with a *P*-value greater than .1 in univariable analysis were sequentially excluded, while those with a *P*-value less than .05 were retained through a stepwise process. The findings were validated through a second multivariable analysis, which included all covariates to account for any subtle effects they may have on the outcomes of interest. The proportional hazards assumption test was tested by plotting the scaled Schoenfeld residuals against time and computing *P*-value for variables included in the model. Univariable and multivariable logistic regression analyses were performed for predictors of distant parenchymal recurrences and LMDs.

A separate nearest one-to-one propensity score matching analysis was performed to balance the groups of VE and non-VE on potential confounders that could affect the likelihood of having VE, namely tumor size, SVZ involvement, distance to SVZ, EOR, age, and preoperative Karnofsky Performance Scale. Baseline demographics and complications were then compared between the matched groups and multivariable regression analyses were performed again.

All statistical analyses were performed using SPSS v27.0 (IBM) and RStudio (2023.12.1 + 412, R Foundation). Graphs were created using GraphPad Prism v10.0 (GraphPad Software). Hazard ratios (HR) with 95% CI and *P*-values were reported for all regression analyses. A *P*-value of ≤.05 was considered statistically significant.

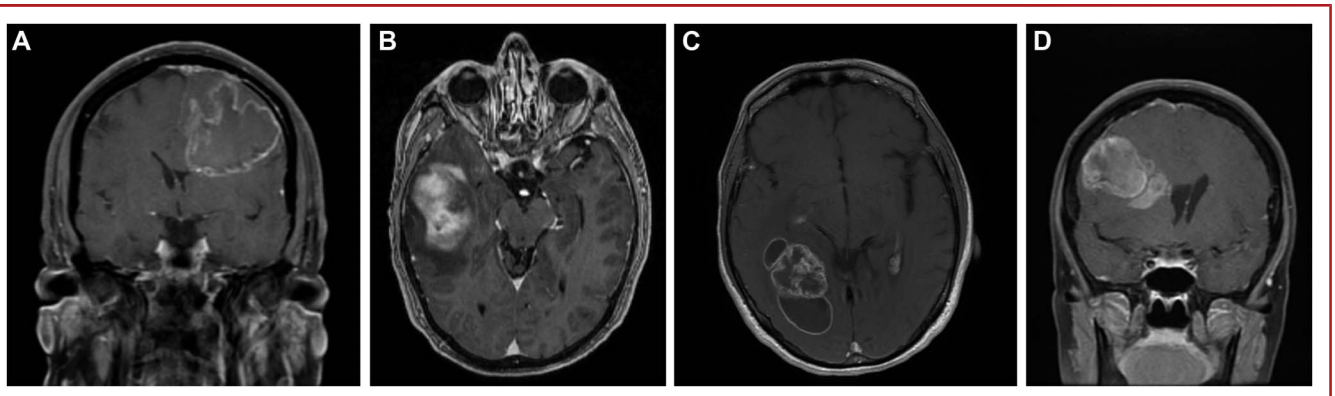

FIGURE 1. *Magnetic resonance images demonstrating glioblastoma contiguous with subventricular zone,* **A-D**.

RESULTS

Patient Characteristics of Unmatched Groups

We identified 765 patients treated for GBM at our institution during the study period. According to the eligibility criteria of this study, we excluded patients whose index operation was performed at an outside institution and data for initial surgery was unavailable (n = 147); patients who underwent biopsy (n = 173), and patients who were either lost to follow-up or elected hospice care immediately after surgery (n = 163).

A total of 282 patients were included in the study and a summary of patient characteristics is shown in Table 1. The median age was 65 years, with 46.1% (n = 130) being female. Most of the patients had an isocitrate dehydrogenase wildtype GBM (n = 223) 79.1%) with an unmethylated O6-methylguanine-DNA methyltransferase (MGMT) promoter (n = 155, 55%). A total of 164 (58.2%) had tumors in contact with the SVZ, and VE occurred during resection in 108 (38.3%) patients. Notably, VE was more common in patients with SVZ-contacting tumors compared with those without contact (57.9% vs 11%, $P < .001$). 46.8% (n = 132) of patients achieved GTR. The GTR rate did not significantly differ between the VE and non-VE groups (51.9% vs 45.9%, $P = .22$). 94% of the patients received postoperative chemotherapy and 97.5% received postoperative radiation, with no significant differences between the VE and non-VE groups.

Postoperative Complications and Outcomes of Unmatched Groups

The median length of stay was 3 days and was significantly longer in the VE group (4 days) compared with the non-VE group (3 days, $P = .008$). Only patients who had VE developed postoperative hydrocephalus (n = 4, 1.4%, $P = .024$) and had external ventricular drain placed (n = 6, 2.1%, $P = .003$) (Table 2). Two patients (0.7%) needed ventriculoperitoneal shunt placement. Intraventricular hemorrhage occurred in 5 patients (2.2%), with no statistical difference between the VE (n = 3, 2.8%) and the non-VE groups (n = 2, 1.1%). Notably, the incidences of distant parenchymal recurrence and LMD were significantly higher in the VE group compared with the non-VE group (63.9% vs 39.7%, $P = .002$, and 39.7% vs 13.2%, $P = .024$).

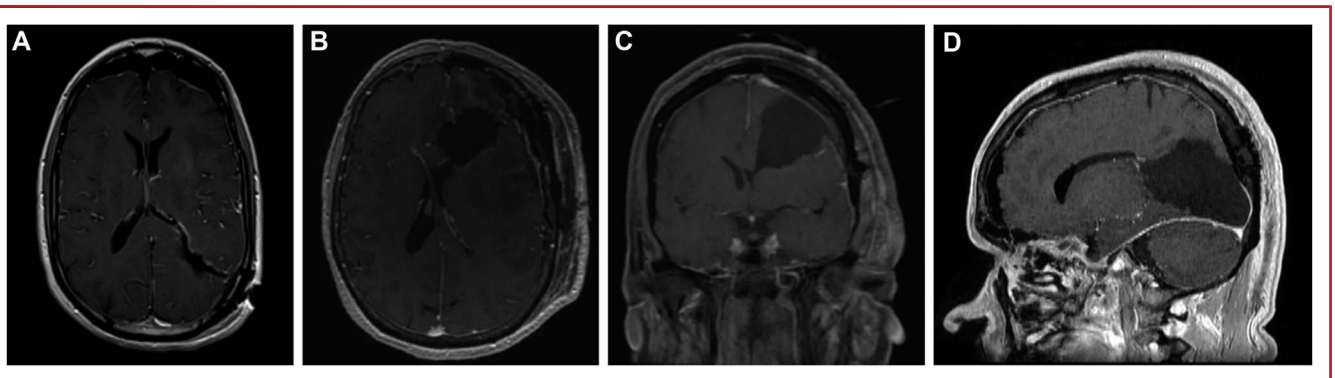

FIGURE 2. *Magnetic resonance images demonstrating ventricular entry,* **A-D**.

TABLE 1. Patient Characteristics

		Unmatched cohorts			Matched cohorts after propensity score analysis		
Variables	**Total**	**VE**	**Non-VE**	***P* value**	**VE**	**Non-VE**	***P* value**
No. of patients	282	108 (38.3)	174 (61.7)		60 (50)	60 (50)	
Age, y	65 [58.8-71]	65 [59-70.8]	65 [58-72]	.807	64 [59.3-69]	67 [59.3-72]	.168
Sex				.902			.574
Female	130 (46.1)	49 (45.4)	81 (46.6)		23 (38.3)	23 (38.3)	
Male	152 (53.9)	59 (54.6)	93 (53.4)		37 (61.7)	37 (61.7)	
Preoperative KPS	90 [80-90]	80 [70-90]	90 [80-90]	.41	90 [80-90]	80 [80-90]	.203
SVZ contact				**<.001**			.596
Yes	164 (58.2)	95 (88)	69 (39.7)		50 (83.3)	50 (83.3)	
No	118 (41.8)	13 (12)	105 (60.3)		10 (16.7)	10 (16.7)	
VE				—			—
Yes	108 (38.3)	—	—		—	—	
No	174 (61.7)	—	—		—	—	
EOR				.22			.851
GTR	132 (46.8)	56 (51.9)	76 (45.9)		24 (40)	22 (36.7)	
Non-GTR	150 (53.2)	52 (48.1)	98 (56.3)		36 (60)	98 (56.3)	
NTR	79 (28)	25 (23.1)	54 (31)		16 (26.7)	20 (33.3)	
STR	71 (25.2)	27 (25)	44 (25.3)		20 (33.3)	18 (30)	
Tumor volume, cm^3	18.4 [8.2-35.4]	26.7 [14.2-46.7]	13.5 [6.5-30.7]	**<.001**	25.1 [15.5-39.14]	24.6 [10.97-35.2]	.213
Operative duration, min	181 [136.5-246.8]	231 [175-302]	165 [126.5-228]	**<.001**	229 [154-270]	187 [140-267]	.453
Length of stay, days	3 [2-5]	4 [2-6]	3 [2-4]	**.008**	3 [2-5.8]	3 [2-4]	.098
IDH 1/2 status				.264			.093
IDH 1/2 wt	223 (79.1)	96 (88.9)	127 (73)		53 (88.3)	42 (70)	
IDH 1/2 mutated	3 (1.1)	0 (0)	3 (1.7)		0 (0)	3 (5)	
Unknown	56 (19.9)	12 (11.1)	44 (25.3)		7 (11.7)	15 (25)	
MGMT promoter methylation	127 (45)	43 (39.8)	84 (48.3)	.18	28 (46.7)	27 (45)	.5
Postoperative chemotherapy	265 (94)	99 (91.7)	166 (95.4)	.184	54 (90)	55 (91.7)	.5
Postoperative radiotherapy	275 (97.5)	105 (97.2)	170 (97.7)	.679	57 (95)	58 (96.7)	.5

EOR, extent of resection; GTR, gross-total resection; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Scale; MGMT, O6-methylguanine-DNA methyltransferase; NTR, near-total resection; STR, subtotal resection; SVZ, subventricular zone; VE, ventricular entry; wt, wild-type.
Bold indicates significance.

The median PFS was 8 months. Patients who had VE during resection had significantly lower median PFS compared with non-VE (6 months [4.3-7.7] vs 9 months [7.5-10.5], $P = .003$ [log-rank]) (Figure 3). Patients who had tumors with SVZ contact also had a significantly shorter PFS (7 months [5.3-8.7] vs 9 months [7.2-10.8], $P = .01$).

The median OS for the entire cohort undergoing resection for newly diagnosed GBM was 16 months. Patients who had VE had significantly lower median OS compared with non-VE (12 months [9.6-14.4] vs 18 months [15.9-20.1], $P < .001$) (Figure 4). Similarly, median OS was shorter in patients who had tumors with SVZ contact compared with tumors without SVZ

TABLE 2. Postoperative Complications and Outcomes

		Unmatched cohorts			Matched cohorts after propensity score analysis		
Variables	**Total**	**VE (n = 108)**	**Non-VE (n = 174)**	***P* value**	**VE (n = 60)**	**Non-VE (n = 60)**	***P* value**
Postoperative hydrocephalus	4 (1.4)	4 (3.7)	0 (0)	**.021**	3 (5)	0 (0)	.244
EVD placement	6 (2.1)	6 (5.6)	0 (0)	**.003**	6 (10)	0 (0)	**.027**
VP shunt placement	2 (0.7)	2 (1.9)	0 (0)	.146	2 (3.3)	0 (0)	.496
Intraventricular hemorrhage	5 (1.8)	3 (2.8)	2 (1.1)	.38	2 (3.3)	2 (3.3)	.691
Distant parenchymal recurrence	136 (48.2)	69 (63.9)	69 (39.7)	**<.001**	44 (73.3)	28 (46.7)	**.005**
Leptomeningeal disease	48 (17)	25 (23.1)	23 (13.2)	**.035**	15 (25)	14 (23.3)	.522

EVD, external ventricular drain; VE, ventricular entry; VP, ventriculoperitoneal.
Bold indicates significance.

contact (13 months [10.6-15.4] vs 19 months [15.9-22], $P < .001$). Notably, when limiting the analysis to tumors with SVZ contact, patients who had VE had significantly shorter survival compared with non-VE (12 months [9.6-14.4] to 17 [12.9-21.1] months, $P < .036$) (Figure 5).

To assess the interaction between EOR and VE in tumors with SVZ contact, where VE is more likely and expected in efforts to maximize EOR, we analyzed 4 permutations of these variables: GTR, and non-GTR, each with and without VE in SVZ contacting tumors (Figure 6). Kaplan-Meier analysis revealed that in VE cases, GTR did not significantly improve median OS compared with non-GTR (14 months [10.2-17.8] vs 10 months [7.5-12.5], $P = .25$). However, in non-VE cases, GTR was associated with a longer median OS compared with non-GTR (25 months [15.7-32.3] vs 13 months [7.8-18.2], $P = .005$). Moreover, GTR without VE had a significantly longer median OS compared with GTR with VE (25 months vs 14 months, $P = .007$) and all possible combinations of EOR and VE (Figure 7A).

Next, we further investigated whether GTR with VE provided any survival benefit compared with NTR with VE and NTR or STR without VE. Patients who underwent GTR with VE had a median OS of 14 months [10.2-17.8], while those with NTR with VE had a median OS of 12 months [4.8-19.2]. Patients with NTR without VE had a median OS of 15 months [9.1-20.8], and those with STR without VE had a median OS of 10.5 months [2.2-17.7]. There were no significant differences in survival between these groups ($P = .55$) (Figure 7B).

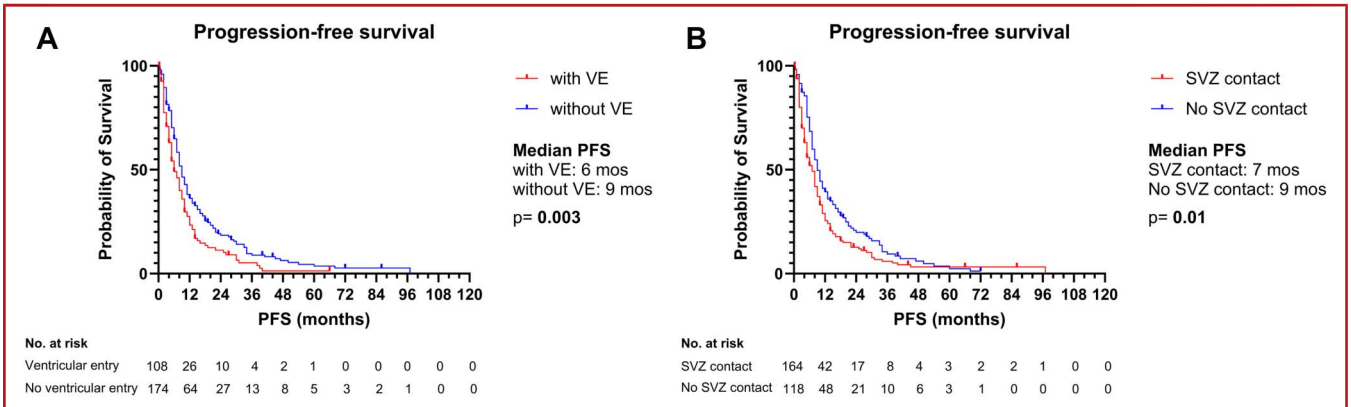

FIGURE 3. *Kaplan-Meier curves demonstrating progression-free survival based on* **A***, ventricular entry and* **B***, SVZ contact. Patients who had VE during resection demonstrated significantly shorter median PFS compared with those without VE (6 months [4.3-7.7] vs 9 months [7.5-10.5], P = .003, log-rank test). Similarly, patients with tumors contacting the SVZ had a significantly shorter PFS (7 months [5.3-8.7] vs 9 months [7.2-10.8], P = .01). PFS, progression-free survival; SVZ, subventricular zone; VE, ventricular entry.*

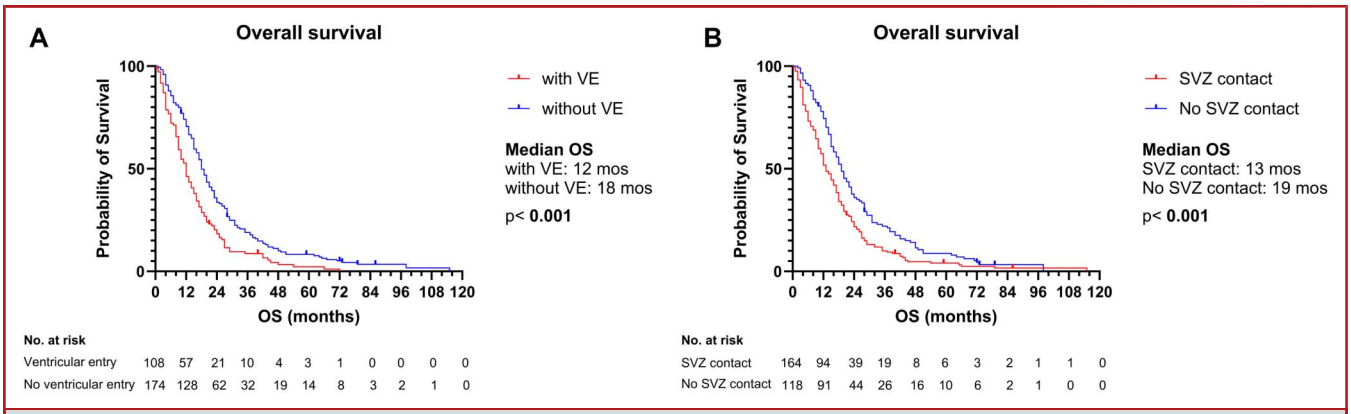

FIGURE 4. *Kaplan-Meier curves demonstrating overall survival based on* **A**, *ventricular entry and* **B**, *SVZ contact. Patients who had VE had significantly lower median OS compared with non-VE (12 months [9.6-14.4] vs 18 months [15.9-20.1], P < .001). Similarly, median OS was shorter in patients who had tumors with SVZ contact compared with tumors without SVZ contact (13 months [10.6-15.4] vs 19 months [15.9-22], P < .001). OS, overall survival; SVZ, subventricular zone; VE, ventricular entry.*

Predictors of Survival, Distant Parenchymal Recurrence, and Leptomeningeal Dissemination

Multivariable Cox regression analyses were performed, including potential prognostic factors such as age, preoperative Karnofsky Performance Scale, EOR, tumor volume, isocitrate dehydrogenase and MGMT status, and history of postoperative chemotherapy and/or radiotherapy to evaluate the influence of VE on OS. An initial stepwise multivariable Cox regression analysis revealed VE as an independent predictor of OS (HR: 1.62 [1.12-2.34], P = .001), along with age, EOR, unmethylated MGMT promoter, postoperative chemotherapy and radiotherapy. These findings persisted in a second multivariable analysis which included all the covariates (Table 3).

Multivariable logistic regression analyses demonstrated VE as the single independent predictor of distant parenchymal recurrence/LMD (HR: 3.07 [1.51-6.22], P = .002) (Table 4).

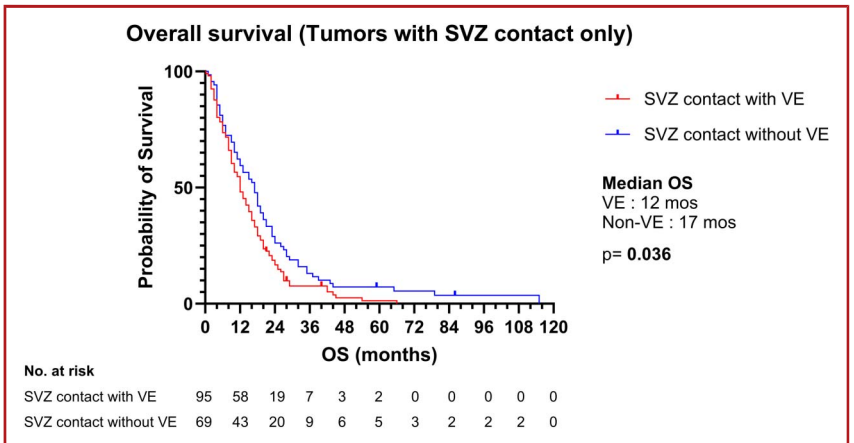

FIGURE 5. *Kaplan-Meier curves demonstrating overall survival based on ventricular entry in tumors contacting the SVZ only, where VE is more likely to maximize extent of resection. Patients with VE had significantly shorter survival compared with non-VE (12 months [9.6-14.4] to 17 [12.9-21.1] months, P < .036). OS, overall survival; SVZ, subventricular zone; VE, ventricular entry.*

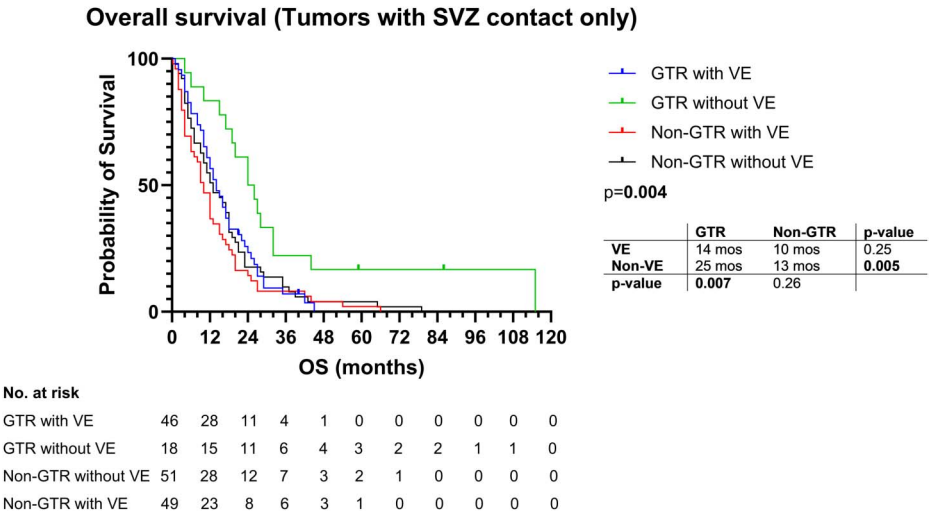

FIGURE 6. *Kaplan-Meier curves showing OS based on VE and GTR in tumors contacting the SVZ. For VE cases, OS did not differ significantly between GTR (14 months [10.2-17.8]) and non-GTR (10 months [7.5-12.5], P = .25). In non-VE cases, GTR was associated with longer OS (25 months [15.7-32.3] vs 13 months [7.8-18.2], P = .005). GTR without VE had significantly longer OS than GTR with VE (25 months [15.7-32.3] vs 14 months [10.2-17.8], P = .007) and all combinations of extent of resection and VE. GTR, gross-total resection; OS, overall survival; SVZ, subventricular zone; VE, ventricular entry.*

Patient Characteristics and Outcomes of Matched Cohorts

After one-to-one nearest neighbor propensity score matching, 60 pairs of cohorts were obtained for comparison. Baseline patient characteristics are shown in Table 1, and postoperative outcomes are summarized in Table 2. The incidence of postoperative hydrocephalus was higher in the VE group compared with non-VE (5% vs 0%, P = .244). Distant parenchymal recurrences and LMDs were more common in the VE group compared with non-VE, with the difference being significant for distant recurrences (DPR: 73.3% vs 46.7%, P = .005; LMD: 25% vs 23.3%, P = .522).

Similar to the multivariable analyses in the unmatched group, VE was found to be an independent risk factor for reduced OS

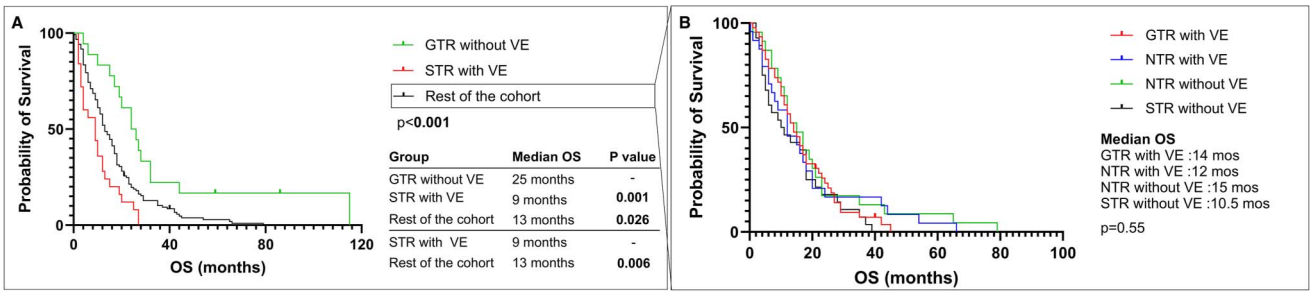

FIGURE 7. *Kaplan-Meier curves detailing the interaction between VE and extent of resection on overall survival in tumors contacting the subventricular zone.* **A**, *Survival comparison among 3 groups: patients who underwent GTR without VE, STR with VE, and a combined group of patients who either had GTR or NTR with VE, or NTR or STR without VE.* **B**, *A focused survival comparison of the combined group from panel A. Patients who underwent GTR with VE had a median OS of 14 months [10.2-17.8], while those with NTR with VE had a median OS of 12 months [4.8-19.2]. Patients with NTR without VE had a median OS of 15 months [9.1-20.8] and those with STR without VE had a median OS of 10.5 months [2.2-17.7]. There were no significant differences in survival between these groups (P = .55). GTR, gross-total resection; NTR, near-total resection; OS, overall survival; STR, subtotal resection; VE, ventricular entry.*

TABLE 3. Multivariable Cox Regression Analyses for Predictors of Overall Survival

	Unmatched cohorts			Matched cohorts after propensity score analysis		
Variable	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
Age	1.03	1.02-1.05	**<.001**	1.01	0.98-1.03	.347
Preop KPS						
80-100	1.33	0.18-9.9	.784	0.4	0.2-0.78	**.007**
50-70	1.42	0.19-10.67	.575	Ref	Ref	Ref
0-40	Ref	Ref	Ref	-	-	-
EOR						
GTR	0.47	0.31-0.703	**<.001**	0.45	0.25-0.83	**.01**
NTR	0.49	0.32-0.74	**<.001**	0.65	0.36-1.17	.15
STR	Ref	Ref	Ref	Ref	Ref	Ref
Tumor volume	1.005	0.99-1.01	.087	1.004	0.99-1.01	.469
SVZ contact	0.96	0.65-1.4	.77	0.54	0.28-1.03	.064
VE	1.62	1.12-2.34	**.001**	1.82	1.15-2.9	**.011**
IDH 1/2 wt	1.56	0.47-5.17	.467	1.69	0.46-6.2	.42
MGMT unmethylated	1.91	1.42-2.57	**<.001**	1.57	0.99-2.47	.053
Postoperative chemotherapy	0.29	0.14-0.62	**.001**	0.24	0.1-0.56	**.001**
Postoperative radiotherapy	0.06	0.02-0.22	**<.001**	0.054	0.011-0.261	**<.001**

EOR, extent of resection; GTR, gross-total resection; HR, hazard ratio; IDH, isocitrate dehydrogenase; KPS, Karnofsky Performance Scale; MGMT, O6-methylguanine-DNA methyltransferase; NTR, near-total resection; STR, subtotal resection; SVZ, subventricular zone; VE, ventricular entry; wt, wild-type.
Bold indicates significance.

(HR: 1.82 [1.15-2.9], P = .011) and distant recurrence/LMDs (OR: 4.11 [1.49-11.4], P = .006) (Tables 3 and 4).

DISCUSSION

This study reconciles findings from multiple studies that link tumor contact with the SVZ to LMD and reduced survival and further demonstrates that VE is an independent risk factor for distant parenchymal recurrences/LMD and decreased survival.

Maximal surgical resection remains the purported cornerstone of treatment for malignant gliomas. Several studies have highlighted critical importance of achieving high EOR in gliomas, leading to its inclusion in treatment guidelines for these tumors.[21,24-26] Radical glioma resections frequently involve entry into the ventricle, which has been suspected of being associated with poor outcomes; however, this hypothesis has been challenged by other studies.[7,8,17-19,21,22,27]

In this study, VE was identified as a key risk factor for decreased OS in GBM patients, after adjusting for well-known prognostic factors and contact with SVZ, a region postulated to harbor tumors with a greater propensity for growth and recurrence.[13,28] Notably, among tumors with SVZ contact, VE remained associated with significantly shorter survival (12 months vs 17 months). While this observation and the mechanisms by which VE leads to poor outcomes remain to be fully elucidated, the association between VE and distant parenchymal recurrences and LMDs is a likely explanation. Our findings indicate that patients with VE had a significantly shorter median PFS and experienced more distant recurrences and LMD compared with those without VE. VE was identified as an independent risk factor for distant recurrences/LMD. Li et al[29] demonstrated that GBM cells could survive and grow in cerebrospinal fluid (CSF) and lateral ventricles. They also reported that when GBM cells were cocultured with cells from the ependymal region, their invasive ability was significantly reduced. The authors inferred that cells from the ependymal region might inhibit GBM invasion through cell interactions. In addition, they observed a subependymal gap between the tumor tissue and the ependymal lining of the lateral ventricles on hematoxylin-eosin and immunohistochemical staining in both pathological biopsies and orthotopic models.

TABLE 4. Multivariable Logistic Regression Analyses for Predictors of Distant Parenchymal Recurrence/Leptomeningeal Disease

	Unmatched cohorts			Matched cohorts after propensity score analysis		
Variable	**OR**	**95% CI**	***P* value**	**OR**	**95% CI**	***P* value**
Age	1.009	0.98-1.04	.52	0.99	0.95-1.04	.712
EOR						
GTR	0.94	0.42-2.1	.88	0.78	0.22-2.76	.7
NTR	0.73	0.32-1.69	.47	0.36	0.1-1.27	.11
STR	Ref	Ref	Ref	Ref	Ref	Ref
Tumor volume	0.99	0.98-1.006	.48	0.98	0.97-1.006	.203
SVZ contact	1.15	0.53-2.5	.73	0.44	0.1-1.86	.262
VE	4.7	2.11-10.4	**<.001**	4.11	1.49-11.4	**.006**
IDH 1/2 wt	0.66	0.05-8.56	.76	1.59	0.1-24.6	.738
MGMT unmethylated	0.88	0.48-1.6	.68	0.96	0.36-2.51	.93
Postoperative chemotherapy	0.25	0.06-2.03	.249	0.47	0.07-3.19	.436
Postoperative radiotherapy	3.48	0.27-43.8	.334	1.94	0.11-34.87	.653

EOR, extent of resection; GTR, gross-total resection; IDH, isocitrate dehydrogenase; MGMT, O6-methylguanine-DNA methyltransferase; NTR, near-total resection; OR, odds ratio; STR, subtotal resection; SVZ, subventricular zone; VE, ventricular entry; wt, wild-type.
Bold indicates significance.

Similarly, several studies noted the presence of a hypocellular gap directly beneath the ependymal layer, then followed by an astrocytic ribbon containing the neural stem cells.[13,30] Conversely, Norton et al[31] showed that GBM cells could physically disrupt the ventricular wall, allowing direct interaction between CSF and tumor tissue in animal models. They suggested that components in the CSF could signal directly to GBM cells in contact with the SVZ and that these tumor cells may also influence cells within CSF. In addition, several studies have indicated that CSF interaction enhances malignancy-promoting transcriptomic pathways in patient-derived GBM cells, resulting in increased survival and migratory capacity of these cells.[31-33] While further research is needed to determine whether the ependymal lining provides a physical and/or molecular barrier to tumor cell spread, these studies indicate that GBM cells can survive and proliferate in CSF while interacting with the SVZ and which may enhance malignant characteristics in these tumors.[29,31-33] Therefore, VE may potentially facilitate, if not trigger, this contact and promote the seeding of malignant glioma cells into the CSF, providing an additional pathway for tumor spread. Multifocal recurrences are believed to further complicate the disease course and lead to poor outcomes.[18,19,21] While recent genomic studies have noted that distant recurrences may result from parallel monoclonal expansions of glioma cells in spatially distinct regions, rather than from tumor spread, several studies have also supported our findings, demonstrating multifocal recurrences with CSF dissemination.[34-39]

Without additional evidence from well-controlled studies, it may be premature to conclude that avoiding VE should be prioritized over maximizing EOR. This is particularly important given that multiple studies have consistently demonstrated a survival advantage associated with GTR over subtotal resections STR. Interestingly, our analysis revealed that GTR did not confer a significant survival benefit over non-GTR when VE occurred, whereas it did in cases where VE was not performed. This finding suggests a complex relationship between GTR, and the risks associated with VE, such as postoperative complications like hydrocephalus and tumor dissemination. These complications could potentially negate the survival benefits typically seen with GTR, which are supported by our findings. Therefore, while achieving maximal EOR should remain a primary goal in GBM resection because of its well-established benefits, the potential for adverse outcomes associated with VE warrants careful consideration. Neurosurgeons must weigh the risks and benefits on a case-by-case basis, understanding that GTR in the presence of VE may not consistently result in the desired survival advantage reported in the literature and could, in fact, lead to worse outcomes.

Limitations

Although the largest study to date on this topic, the data are limited by the inherent bias of its retrospective and single-institutional design. Prospective, multicenter studies may provide more generalizable and robust conclusions on the impact of

VE on survival in patients with GBM. In addition, CSF was not sampled after VE to determine whether tumor cells were disseminated and LMD was solely classified based on classical imaging appearance. However, cytology alone should not be used to rule out dissemination, especially if the sample was obtained through lumbar puncture because it has been reported to lack sensitivity in several studies.[34]

CONCLUSION

This study identifies VE as a significant independent risk factor for distant parenchymal recurrences and diminished survival in patients with GBM, with evidence linking it to reduced OS and PFS. While maximizing tumor resection is critical, neurosurgeons should be mindful of the potential for poorer survival outcomes with VE. The findings of this study warrant further investigation through multi-institutional studies and randomized clinical trials. In addition, future research should focus on the properties of the SVZ, exploring its role in recurrence, aggressive prognosis, and potential as a target for new treatment strategies. Our treatment approaches and surgical goals for tumors involving the SVZ—where VE is more common, and cells exhibit a higher propensity for growth and recurrence—may need to be re-evaluated.

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COMMENTS

I read with interest this study of the impact of ventricular entry during glioblastoma resection and potential association with reduced survival and increased risk of distal recurrence. This has long been held as a belief by some neurosurgeons that ventricular entry could have a negative impact on patient outcome. This study further lends support to that suspicion. Further detailed analysis of this nature, and inclusion of larger populations of patients could help to further refine this conclusion, but this certainly is worth consideration in a surgeon's decision making. One must weigh whether to pursue radical resection if it would result in significant ventricular entry as this may have a negative impact upon patient survival. Whether this would be true for lower grade gliomas, metastases, or other tumors or not also would be of interest and could be worthy of further study.

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