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Relationship of glioblastoma multiforme to the subventricular zone is associated with survival

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The subventricular zone (SVZ) lines the lateral ventricles and represents the origin of neural and some cancer stem cells. Tumors contacting the SVZ may be more invasive with higher potential to recruit migratory progenitor cells. Our specific aim was to determine whether SVZ involvement in glioblastoma multiforme (GBM) is associated with a higher recurrence rate and shorter overall survival. MR imaging and clinical data from 91 patients with GBM treated at our institution were retrospectively reviewed. Tumors were classified as type I if the contrast-enhancing lesion contacted both the SVZ and cortex on pre-operative MRI, type II if only the SVZ was involved, type III if only cortex was involved, and type IV if the lesion did not contact either the SVZ or cortex. Progression-free survival (PFS) and overall survival were estimated based on Kaplan-Meier calculations. When comparing type I tumors with types II-IV, only 39% of patients with type I tumors were free of recurrence and alive at 6 months, significantly fewer than for all other types combined (67%; $P = .01$). PFS at 6 months was also less, at only 47% among patients with SVZ-positive tumors, compared with 69% in the SVZ-negative group ($P = .002$). Patients with SVZ involvement also demonstrated a more rapid time to progression, compared with those not involving the SVZ ($P = .003$). Patients with GBM involving the SVZ have decreased overall survival and PFS, which may have prognostic and therapeutic implications.

Keywords: glioblastoma multiforme, subventricular zone, survival.

Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor in adults and carries a poor prognosis, with survival of approximately 1 year. Initially thought to be a single disease process, GBM is now considered to be a clinically, histopathologically, and radiographically heterogeneous disease. Understanding the variation in patterns of progression and survival may help in guiding therapy.

Recent evidence suggests that the heterogeneity seen in GBM may be related to the cells of origin, which have stem cell–like characteristics.[1–3] Neural stem cells line the lateral ventricles in the subventricular zone (SVZ) and recruitment of these progenitor cells may play a role in the aggressive behavior encountered in GBM. We have previously proposed a classification system for GBM based on the spatial relationship of the contrast-enhancing lesion to the subventricular zone, which we found to be related to variable patterns of multifocality and recurrence.[1] The classification scheme divides patients into 4 subtypes (Fig. 1, used with permission[1]). Patients with type I GBM have tumors in which the contrast-enhancing lesion contacts both the SVZ and the cortex. Patients with type II GBM have tumors that contact the SVZ only and spare the cortex, type III tumors contact the cortex and spare the SVZ, and type IV tumors spare both the cortex and the SVZ. We previously demonstrated that type I tumors involving the SVZ and cortex tend to more often be multifocal at diagnosis and also at recurrence, compared with types II-IV (Figures 2 and 3). Our aim in the current study was to expand on these results to determine whether there is a survival difference among the subtypes. Specifically, the purpose of our study was to determine whether the presence of SVZ involvement in GBM is related to shorter overall survival and progression-free survival (PFS).

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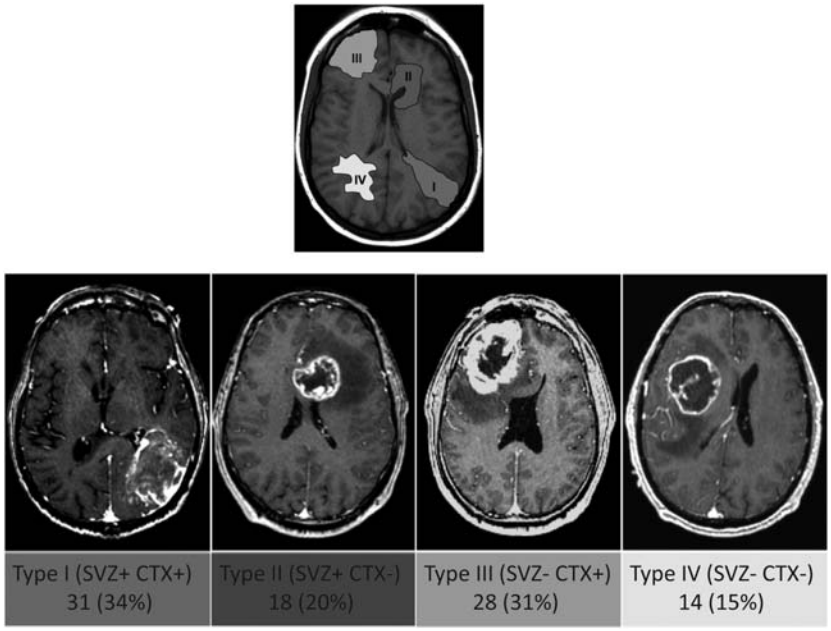

Fig. 1. Classification of GBM into types I-IV, based on MR imaging. Type I tumors contact both the SVZ and the cortex, type II tumors involve only SVZ, type III tumors involve only cortex, and type IV do not contact either SVZ or cortex. Used with permission.[1]

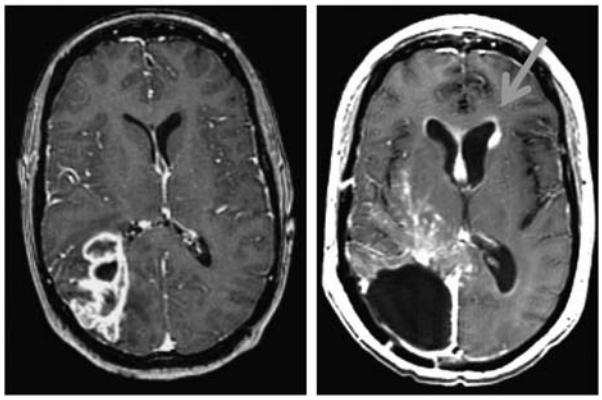

Fig. 2. Recurrence pattern in a 46-year-old woman with type I GBM after surgical resection and chemoradiation. Image on the left demonstrating pre-operative tumor appearance with the contrast-enhancing lesion contacting both the SVZ and the cortex. Image to the right depicting a common recurrence pattern in type I tumors, with both local recurrence and remote SVZ recurrence as delineated by the arrow adjacent to the frontal horns.

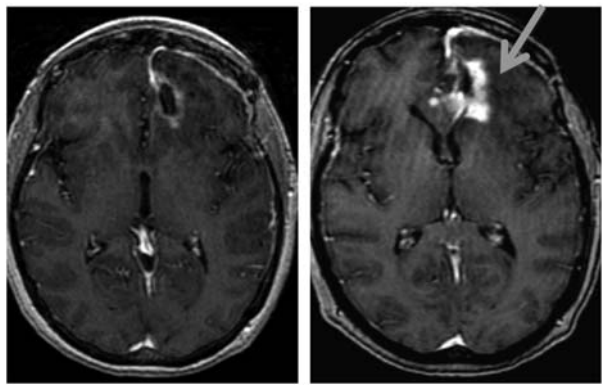

Fig. 3. Recurrence pattern in a 57-year-old man with type IV GBM. Both images demonstrate the typical pattern seen in type IV tumors with recurrence at the site of surgical resection.

Materials and Methods

Patient Population

We performed an Institutional Review Board–approved retrospective review of 91 patients with GBM who underwent surgery, radiation, and chemotherapy at our institution from January 2000 through October 2008. Patients were included in the study if their pre- and post-operative MR imaging was either performed at our institution or available on the picture archiving and communication system (PACS) for review. All patients subsequently received external beam therapy and Temodar. In addition, all patients were enrolled in 1 of 3 clinical trials in which they were receiving a single experimental agent, none of which were found to affect outcome.[4–6] Bevacizumab was not part of the initial regimen in any of these studies. Patients were excluded from the study if pre-operative or follow-up imaging was not available for review. Follow-up was through July 2012.

MRI Characteristics and End Points

Tumors were classified as involving the SVZ if the contrast-enhancing lesion contacted the lining of the

ventricle. Similarly, the tumors were classified as involving cortex if the contrast-enhancing lesion contacted the cortex. Patterns of recurrence were evaluated and considered to involve remote SVZ if the recurrent contrast-enhancing disease was >2 cm from the resection cavity and in contact with the SVZ. Size of the contrast-enhancing lesion was calculated as area based on 2-dimensional measurements (calculated as area of an ellipse) using longest anteroposterior (AP) and transverse dimensions measured on axial MR images.

Other parameters evaluated included apparent diffusion coefficient (ADC) values and cerebral blood volume (CBV) measurements prior to treatment if diffusion-weighted and perfusion imaging were available. ADC values were obtained by drawing a region of interest (ROI) conforming to the margins of the contrast-enhancing lesion and ensuring accurate values by comparing this numerical value with the vitreous of the eye. CBV was calculated using negative enhancement integral with the area under the signal intensity–time curve representing CBV. CBV measurements were obtained by drawing an ROI in the tumor and were standardized to an ROI in the contralateral white matter producing relative CBV values.

Statistical Analysis

Overall survival was measured from date of diagnosis to date of death or date of last contact if alive. All patients were enrolled in clinical trials, with disease progression based on clear radiographic progression or progressive clinical symptoms. The probability of overall survival and PFS was estimated using the Kaplan-Meier product limit method. Comparison of subsets for each outcome was performed using the log rank test. Analysis of variance methods with post hoc tests were used to compare the mean values for tumor size, ADC, and CBV across subtypes.

Results

Patient Population

Ninety-one patients who underwent surgery for GBM were analyzed. Fifty-nine patients (65%) underwent partial resection, and 32 patients (35%) received gross total resection of their tumor (see Table 1).

Of the 91 patients, 31 (34%) had type I tumors contacting the SVZ and cortex, 18 (20%) had type II tumors contacting the SVZ and sparing cortex, 28 (31%) had type III involving the cortex and sparing the SVZ, and 14 (15%) had type IV tumors that spared both cortex and SVZ. Forty percent of the patients had multifocal disease on initial MRI (see Table 1).

Progression and Survival

Of the 91 patients analyzed, 76 patients progressed either by follow-up imaging or clinically and 15 patients did not progress. Of the 76 patients who progressed, 75 patients had follow-up MRIs that could be evaluated. One patient at the time of progression had an MRI at an outside institution and volume measurements could not be made on the hard copy images at the PACS workstation. Of the 75 evaluable patients with progression, 59 (79%) demonstrated SVZ involvement at the time of progression. Fifteen of these patients had both local and distant SVZ involvement. Patients whose initial tumors involved the SVZ (type I and II tumors) were more likely to have SVZ involvement at the time of progression, with 39 (89%) of 44 patients demonstrating SVZ involvement. In contrast, of the 31 patients whose initial tumors did not involve the SVZ (type III and IV) and progressed, only 20 (65%) demonstrated SVZ involvement at progression ($P = .02$). Patients with SVZ involvement also demonstrated a more rapid time to progression than did those without SVZ involvement ($P = .003$).

PFS at 6 months estimated from the Kaplan-Meier analysis was 39% among type I, 61% among type II,

Table 1. Characteristics of study population

Parameter	All patients	Type I (SVZ+,CTX +)	Type II (SVZ+,CTX −)	Type III (SVZ−CTX +)	Type IV (SVZ−,CTX −)
Patients					
No. (%)	91	31 (34)	18 (20)	28 (31)	14 (15)
Sex					
Male	61	19	13	20	9
Female	30	12	5	8	5
Age (years, mean ± SD)	54.5 ± 11.3	54. 3 ± 11.2	55.9 ± 14.3	54.6 ± 9.9	52.5 ± 11.0
No. patients with multifocal GBM (%)	36 (40)	15 (48)	5 (28)	12 (43)	4 (29)
CEL area, cm^2 (mean ± SD)	12.5 ± 8.2	15.6 ± 9.1	10.6 ± 5.9	13.4 ± 8.3	6.3 ± 4.1
Extent of resection (%)					
Gross total	32 (35)	5 (16)	7 (39)	17 (61)	3 (21)
Subtotal	59 (65)	26 (84)	11 (61)	11 (39)	11 (79)

71% among type III, and 64% among type IV patients recurrence-free or alive ($P = 0.04$) (see Fig. 4). When patients with type I and II (SVZ-positive) tumors were compared with those with types III and IV (SVZ-negative), the PFS estimate at 6 months was also less for SVZ-positive than for SVZ-negative patients (Kaplan-Meier 6 month estimates: 47% vs 69%; $P = .002$) (see Fig. 5). When comparing type I tumors with types II-IV, the PFS at 6 months among patients with type I tumors (SVZ and cortex positive) was only 39%, significantly less than for all other types combined (67%; $P = .01$).

Of the 91 patients, 74 had died and 17 were alive at the time of last update in July 2012. The Kaplan-Meier analysis was used to estimate the probability of surviving at 2 years. The probability estimate at 2 years was 17% among patients with type I tumors, compared with 28% among type II, 43% among type III, and 50% among patients with type IV tumors ($P = .053$). Overall survival at 2 years was 23% among patient with tumors involving the SVZ, compared with 48% among patients with tumors not involving SVZ ($P = .002$) (Fig. 6). At 2 years, 17% of patients with type I tumors survived, compared with 40% for all other types combined ($P = .02$).

Other Parameters

Size.—The tumor size ranged from 0.8 to 47.6 cm^2 for the entire study sample, with a mean of 12.5 cm^2 and median of 10.4 cm^2. When SVZ-positive tumors were compared with SVZ-negative tumors, no difference in tumor size was observed ($P = .12$). However, type IV tumors were found to be significantly smaller than all other types ($P = .002$).

ADC and CBV.—Because of differences in scan technique, not all patients had diffusion-weighted or perfusion imaging performed. Among the patients in our study population, 53 of 91 had ADC values for their tumors and 52 had CBV measurements available. No statistically significant differences were found among the 4 types in ADC values ($P = .12$) or in CBV measurements ($P = .61$) for those evaluated.

Extent of Resection

In our patient population, there was a significant association between the subtype and extent of surgery (Fisher's exact test, $P = .002$). For each subtype except type III, a greater proportion of patients had subtotal resection. For patients with type III tumors, in contrast, the majority (61%) underwent gross total resection. There was a significant association between SVZ involvement and extent of resection (Fisher's exact test, $P = .028$), with 76% of patients with type I and II tumors receiving subtotal resection and 24% undergoing gross total resection. In comparison, in patients with type III and IV tumors, 52% underwent subtotal resection, and 48% underwent gross total resection. The data were further analyzed to determine whether these differences in extent of resection had an impact on survival. In our

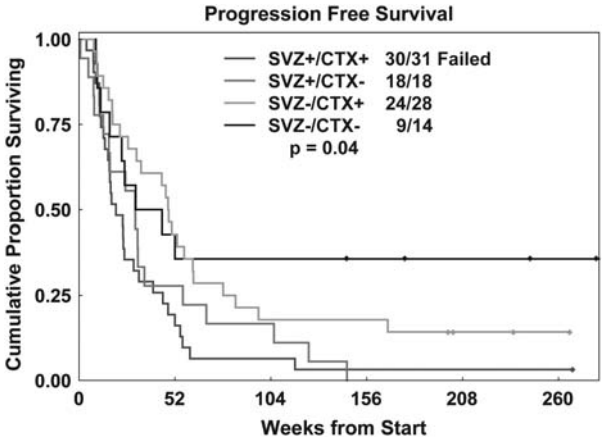

Fig. 4. PFS curve for all patients with GBM (types I-IV).

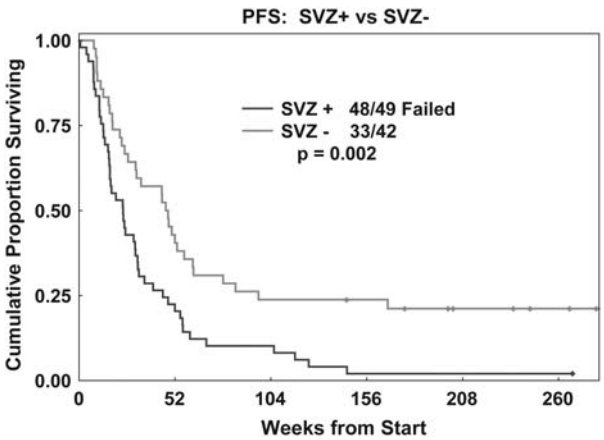

Fig. 5. PFS curve comparing patients with SVZ-positive (types I and II) and SVZ-negative (types III and IV) disease.

Fig. 6. Kaplan-Meier curve demonstrating survival difference between SVZ-positive and SVZ-negative tumors.

study, SVZ contact was found to be an independent predictor of survival, regardless of resection. The extent of resection did not translate into a difference in either overall survival or PFS ($P = .24$ and $P = .18$, respectively). To consider the effect of the type of resection with subventricular zone and cortical involvement, only the type was a significant independent predictor of outcome. This was analyzed using Cox's proportional hazards model with a forward stepwise approach. When the subtypes were analyzed using type I as the reference, both type II ($P = .01$) and type III ($P = .01$) significantly differed from type I, but extent of resection did not. This indicates the significant difference between tumors that are SVZ-positive and those that are SVZ-negative in relation to PFS.

Analysis of Other Subgroups

When patients with cortex-positive and cortex-negative tumors were compared, no statistically significant differences in PFS were noted (6 month estimates: 54% vs 63%; $P = .50$). When type IV tumors were compared with all other types (I-III) combined, a statistically significant difference in PFS was noted (6 month estimates: 64% for type IV tumors vs 56% for all others; $P = .04$).

Discussion

Our results demonstrate that, when GBMs involve the SVZ, regardless of cortical involvement, patients progress more quickly and have decreased survival, compared with those with tumors not contacting the SVZ. In addition, patients with type I tumors, contacting both the SVZ and cortex, fare worst of all. These findings suggest a significant relationship between initial involvement of the SVZ and overall prognosis. We were specifically interested in addressing the contrast-enhancing lesion's relationship to the SVZ, because this evaluation is least variable in interpretation among neuroradiologists.

Throughout adulthood, the SVZ maintains the ability to produce neurons, with previous evidence[7,8] suggesting that the recruitment of these cells adjacent to the lateral ventricles may account for the invasiveness of gliomas. In animal studies,[9–11] the SVZ demonstrates increased susceptibility to tumorigenesis, compared with cortical regions. The aggressive behavior of the specific subtypes of GBM that contact the SVZ may be related to the recruitment of neural stem cells from the SVZ that have a propensity for invasive proliferation. This hypothesis is supported by results of animal model experiments involving viral transformation of SVZ cells leading to tumor formation.[12] A previous study by Kappadakunnel et al did not find that tumors contacting the subventricular zone were more likely to be stem cell derived.[13] However, as the group noted, this may have been related to their small sample size, which included only 25 patients with tumors contacting the SVZ.

We have previously shown that type I tumors are more likely to demonstrate recurrent tumor at locations distant from the initial lesion (Figure 2),[1] which may, in part, account for the poorer prognosis in this group from a treatment standpoint.

Extent of resection, which often depends on tumor size, the patient's neurological status, and experience of the neurosurgeon, has been shown to be an independent predictor of patient survival.[14] In our patient sample, no statistically significant difference in size was found between SVZ-positive and SVZ-negative tumors, suggesting that SVZ contact is an independent predictor of survival regardless of tumor size. In a previous observational study of 52 patients, Chaichana et al. compared patients with GBMs whose contrast-enhancing lesion contacted the SVZ with those with lesions not contacting the SVZ and matched the groups for factors associated with survival, such as age, Karnofsky performance score, tumor size, gross total resection, and Temodar chemotherapy.[11] They found a statistically significant difference between the groups, with SVZ contact associated with decreased survival. A similar study in a larger patient population of 393 found 30% decreased survival among patients with GBM in a periventricular location.[15]

One limitation of our study is the variable treatment regimens for the patients with regard to the types of salvage therapy received later in the course of their disease, which was not consistently collected; therefore, we were not able to analyze. This potential heterogeneity in treatment may have affected our evaluation of patient survival. A second limitation is the small subset of patients with type IV tumors (15%), who had significantly smaller tumors and significantly longer survival ($P = .01$).

Our study demonstrates that GBMs with both SVZ and cortical involvement and SVZ contact alone result in shorter PFS and overall survival. Thus, SVZ involvement may serve as a prognostic indicator for patients who should be treated more aggressively early in their disease. These patients may benefit from therapy specifically targeting the SVZ.

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Conflict of interest statement. None declared.

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