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RESEARCH ARTICLE

Influence of glioblastoma contact with the subventricular zone on survival and recurrence patterns

S. Comas[1] · E. Luguera[2] · J. Molero[2] · C. Balaña[3] · A. Estival[3] · S. Castañer[4] · C. Carrato[5] · C. Hostalot[6] · P. Teixidor[6] · S. Villà[1,7]

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Abstract

Background There is growing evidence that the subventricular zone (SVZ) may be involved in both the initiation and progression of glioblastoma (GB). We aimed to assess tumor proximity to the SVZ as a potential prognostic factor in GB.

Method Retrospective study of 133 patients diagnosed with primary GB who underwent surgery followed by temozolomide-based chemoradiation between 2010 and 2016. All lesions were classified according to their anatomic relation with the SVZ. We determined the effect of tumor contact with the SVZ on progression-free survival (PFS), overall survival (OS), type, and patterns of recurrence.

Results At a median follow-up of 18.6 months (95% CI 15.9–21.2), PFS and OS were 7.5 (95% CI 6.7–8.3) and 13.9 (95% CI 10.9–16.9) months, respectively. On the univariate analyses, initial contact with the SVZ was a factor for poor prognosis for both PFS (6.1 vs. 8.7 months; $p=0.006$) and OS (10.6 vs. 17.9 months; $p=0.037$). On the multivariate analysis, tumor contact with the SVZ remained statistically significant for PFS, but not OS. Patients with SVZ-contacting tumors presented a higher rate of aggressive clinical progression (30.9% vs. 11.3%; $p=0.007$) and contralateral relapse patterns (23.4% vs. 9.1%; $p=0.048$).

Conclusions Our results suggest that glioblastoma contact with the SVZ appears to be an independent prognostic factor for poor PFS. The presence of an SVZ-contacting tumor was associated with more aggressive recurrences and a higher rate of contralateral relapses. These findings suggest that this variable may be a new prognostic factor in glioblastoma.

Keywords Glioblastoma · Subventricular zone · Tumor location · Prognostic factor · Cancer stem cell

✉ S. Villà
svilla@iconcologia.net

S. Comas
scomas@iconcologia.net

E. Luguera
eluguera@iconcologia.net

J. Molero
jmolero@iconcologia.net

C. Balaña
cbalana@iconcologia.net

A. Estival
aestival@iconcologia.net

S. Castañer
sara.castaner@idi.gencat.cat

C. Carrato
ccarrato.germanstrias@gencat.cat

C. Hostalot
chostalot.germanstrias@gencat.cat

P. Teixidor
pilarteixidor.germanstrias@gencat.cat

1 Radiation Oncology, Institut Català D'Oncologia, c/ del Canyet SN, 08916 Badalona, Catalonia, Spain

2 Physics, Institut Català D'Oncologia, Badalona, Catalonia, Spain

3 Medical Oncology, Institut Català D'Oncologia, Badalona, Catalonia, Spain

4 Neuroradiology, Institut de Diagnòstic Per La Imatge, Badalona, Catalonia, Spain

5 Pathology. Hospital Universitari Germans Trias I Pujol, Badalona, Catalonia, Spain

6 Neurosurgery. Hospital Universitari Germans Trias I Pujol, Badalona, Catalonia, Spain

7 Universitat Autònoma de Barcelona, Badalona, Catalonia, Spain

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Background

Glioblastoma (GB) is the most common and most aggressive type of primary central nervous system tumor in adults, with an incidence of 3.2 cases per 100,000 inhabitants [1]. Several studies suggest that the initiating cells in GB could arise from normal neural stem and progenitor cells through the acquisition of a series of tumor-inducing alterations, thus leading to uncontrolled proliferation [2–4]. There is growing evidence that the subventricular zone (SVZ) may be involved in both the initiation and progression of GB [5].

The SVZ is located in line with and sidelong to the lateral ventricles (LV), and contains multiple cell types, most notably neural stem cells (NSC) [6, 7]. Research in animal models has shown that brain areas with a higher proliferative index are more sensitive to oncogenesis [8–11]. Piccirillo et al. [12] found that the SVZ was a source of cancer stem cells underlying tumor formation, resulting in the first direct evidence for the role of the SVZ in gliomagenesis. Numerous studies have shown that patients whose lesions maintained initial anatomical contact with the SVZ have worse survival outcomes and more aggressive patterns of relapse [13–18]. These findings underscore the need to gain a better understanding of the role of the SVZ in GB as a potential source of cells capable of mediating initiation, promotion, and relapse through tumor repopulation. Likewise, more information is needed to determine whether tumor contact with the SVZ could be considered a prognostic factor in patients with GB.

In this context, the aim of this retrospective study was to determine the influence of SVZ-contacting tumors on survival in patients diagnosed with primary GB and treated with surgical resection or biopsy and radiochemotherapy. We also sought to determine the prognostic value of the presence of an SVZ-contacting tumor on patterns of recurrence.

Methods

Patient selection

We retrospectively identified all patients diagnosed with and treated for primary GB at our institution (Catalan Institute of Oncology in Badalona, Barcelona) from January 2010 to July 2016. A total of 133 patients were identified, all of whom were included in the prospective glioblastoma genomics project in Catalonia (GLIOCAT).

Study inclusion criteria were as follows: (1) histological diagnosis of GB, (2) completed full course of radiotherapy (RT), and (3) availability of magnetic resonance images (MRI) obtained preoperatively and at the time of initial relapse after completing RT or upon clinical progression. Classical prognostic factors of GB were recorded.

Imaging data

Preoperative MRI data [contrast-enhanced T1-weighted imaging (T1WI) and FLAIR/T2 images] were assessed to determine the presence of focal *vs*. multifocal tumors at diagnosis and to assess the anatomical relationship between the tumor and the SVZ and cerebral cortex. Multifocal disease was defined as multiple discrete areas of tumor on contrast-enhanced imaging embedded with, or connected by, T2/FLAIR signal abnormality.

SVZ-contacting tumors were defined as tumors whose border on contrast-enhanced MRI was located at a distance of 0 mm from the SVZ, following the definition used in similar studies [14–20]. All lesions were catalogued according to the classification system developed by Lim et al. [15] with regard to anatomical contact with the SVZ and/or cerebral cortex. Prognostic groups were defined as follows: group 1: lesions contacting both the SVZ and cerebral cortex; group 2: lesions contacting the SVZ but not the cerebral cortex; group 3: lesions contacting the cerebral cortex but not the SVZ; group 4: lesions not contacting either of these structures. All lesions were classified too as SVZ-contacting or SVZ-not contacting tumors.

The SVZ was defined on computed tomography (CT) treatment planning as the area comprising a lateral margin of 4 mm along the LVs, including both temporal horns [21] (Fig. 1).

Treatment

All patients underwent biopsy or surgical resection of the tumor followed by adjuvant temozolomide (TMZ)-based chemoradiation, as described elsewhere [22–24]. Two different radiotherapy schemes were applied, as follows: in most patients, RT consisted of focal RT up to 60 Gy delivered in 30 fractions (2 Gy/fr); in elderly patients or patients with low performance status, the scheme was 40 Gy in 15 fractions (2.66 Gy/fr).

Patterns of recurrence

Follow up MRIs were taken every 3 months and relapse diagnosis was based on RANO criteria. Patients with radiological progression on one of the follow-up MRIs were considered to present "radiological progression". Patients who presented a sudden worsening of their clinical condition without being able to reach confirmatory MRI were

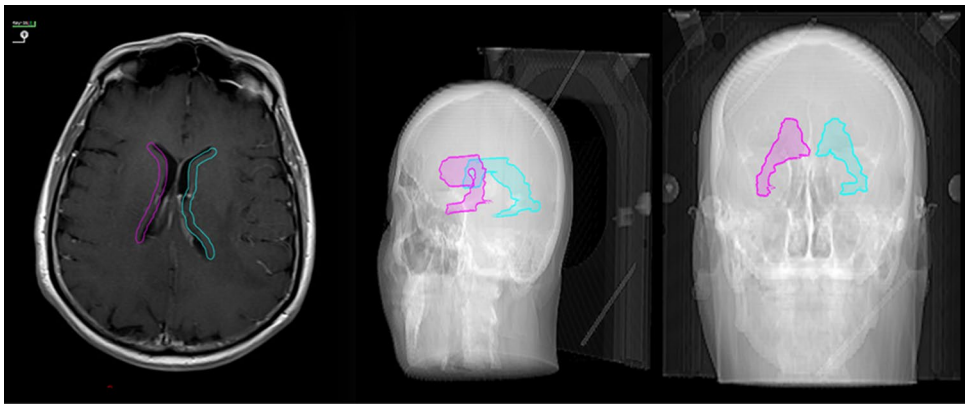

Fig. 1 Subventricular Zone design on CT treatment planning. It was defined as the area comprising a lateral margin of 4 mm along the LVs, including both temporal horns

classified as presenting "clinical progression", which was considered to indicate a more aggressive type of progression.

Radiological recurrences were classified as local, ipsilateral, ipsilateral + contralateral, contralateral, or local + ipsilateral [17]. The recurrence was classified as focal or multifocal, and either contralateral or not contralateral based on the disease extension.

Contrast-enhanced T1WI and FLAIR/T2 MRI were co-registered with the radiation treatment to classify the relapse according to RT isodose lines as follows: central (within the 95% dose), in-field (80–95% isodose), marginal (20–80% isodose), and distal (beyond the 20% isodose) [25] (Fig. 2).

Statistical analyses

The data are expressed as frequencies and percentages for categorical variables and as means or medians with confidence intervals (CI) for continuous variables. The Chi-square test was used to perform group comparisons for qualitative data.

Progression-free survival (PFS) was defined as the time elapsed between surgery and the first radiologically confirmed relapse after completing RT or the date of clinical relapse confirmed by a physician. The overall survival (OS) was defined as the time between the date of surgery and death. Patients who remained progression free or alive were censored at the time of their last follow-up to determine the OS rate. The Kaplan–Meier estimation method was used to create survival tables and curves, with the log-rank test used to perform comparisons.

A univariate analysis was carried out to identify prognostic factors for PFS and OS; the Kaplan–Meier and log-rank test were used to evaluate categorical variables while Cox regression models were performed for continuous variables. A multivariate analysis was also performed, using the Cox regression model.

The threshold for statistical significance was set at $p < 0.05$. The statistical analysis was carried out using the IBM-SPSS Statistical program for Windows, v.24.0 (IBM Inc., Armonk, NY, USA).

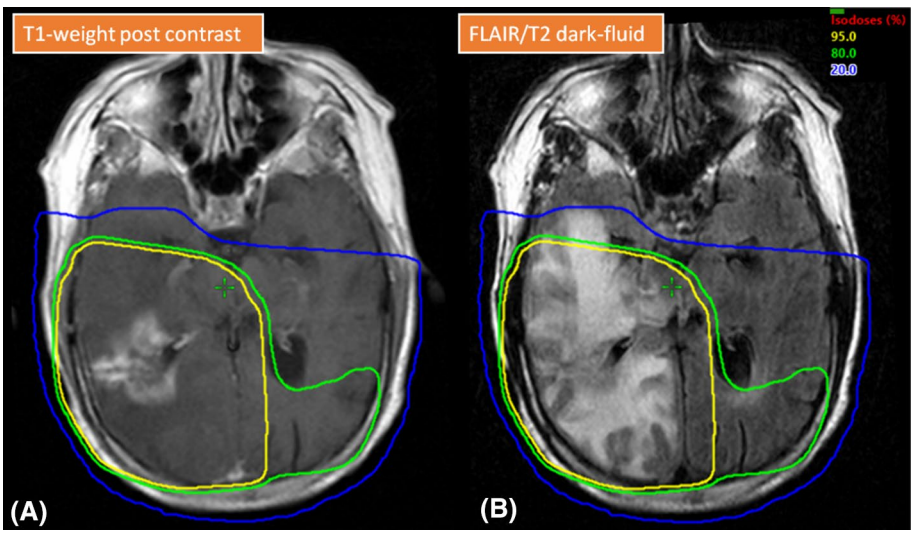

Fig. 2 Progression pattern according to radiation treatment isodoses. **a** T1-weight post contrast MRI. **b** Images FLAIR/T2 dark fluid MRI. Yellow line marks 95% isodose area; green line marks 80% isodose area; blue line marks 20% isodose area

Results

Patient characteristics

A total of 133 consecutively treated patients were included. At a median follow-up of 18.6 months (95% CI 15.9–21.2), 97.7% of the patients presented disease progression. The patients' clinical and radiological characteristics are shown in Table 1. The pattern of disease progression according to RT isodoses was evaluated in the 101 patients classified as presenting radiological progression (for one patient only contrast-enhanced T1WI images were available). Relapse classification based on the RT isodoses was also adapted to the FLAIR/T2 images (Fig. 2).

Analysis of survival and relapse pattern

Patients with lesions not contacting the SVZ presented a higher median PFS (8.7 vs. 6.1 months, $p = 0.006$) as well as a higher median OS (17.9 vs 10.6 months, $p = 0.037$) as compared to those patients with SVZ-contacting tumors.

Patients in groups 1 and 2 (Lim's classification) presented, respectively, a median PFS of 7 (95% CI 6–8.1) and 5.8 months (95% CI 5.1–6.5) versus 8.8 (95% CI 7.6–10) and 8.7 months (95% CI 4.8–12.7), respectively, in groups 3 and 4 ($p = 0.036$). Groups 1 and 2 also presented a lower median OS [12.9 months (95% CI 8.5–17.3) and 9.6 months (95% CI 7.4–11.7)] compared to groups 3 and 4, with a median OS of 18.7 (95% CI 13.7–23.8) and 16.1 months (95% CI 1.3–30.9), respectively ($p = 0.028$) (Fig. 3).

On the multivariate analysis (Table 2), contact with the SVZ was a prognostic factor for worse PFS both using dichotomic ($p = 0.041$) and Lim's classification ($p = 0.047$). Other significant prognostic factors for PFS were methylated status of MGMT (*O6-metilguanine-DNA-metiltransferase*) promoter and administration of concomitant TMZ. The following variables were significant prognostic factors for improved OS: gross total resection (GTR) against biopsy; methylation of MGMT promoter; concomitant TMZ; and age ≤ 65 years. However, the absence of tumor contact with the SVZ was not a significant prognostic factor for OS.

Subanalysis of the population treated with a 60 Gy scheme ($n = 109$), showed in the final multivariate analysis that the classification in the 4 Lim subgroups [being reference category group 4, HR with a 95%CI are: 1.4 (0.7, 2.8) for group 1; 0.8 (0.4, 1.6) for group 2 and 0.6 (0.3, 1.1) for group 3; p 0.032] and methylation status [2.9 (1.8, 4.5); $p < 0.001$] were independent prognostic factor for PFS while the dichotomic classification in SVZ-contacting or SVZ-not contacting tumors [1.5 (0.99, 2.3); p 0.058] and methylation status [2.6 (1.7, 3.9); $p < 0.001$] presented a trend and a statistical significance respectively, as independent prognostic factors for PFS.

SVZ-contacting lesions presented a significantly higher proportion of aggressive clinical progression versus non-contacting lesions (30.9% vs. 11.3%) ($p = 0.007$). The same effect was observed for Lim's group 1 (37.9%) and group 2 (25.6%) versus groups 3 (7.1%) and 4 (20%) ($p = 0.017$).

Group 2 lesions were associated with the highest rate of multifocal involvement at diagnosis (35.9%), followed by group 4 (33.3%) ($p = 0.022$). Lesions not contacting the cerebral cortex were associated with higher rate of multifocality at diagnosis than cortex-contacting lesions (35% vs. 13.7%, $p = 0.004$).

At relapse, we found no significant association between Lim's classification nor between contact status with the SVZ and focality. The anatomical relation between the tumor and the SVZ had no impact on the relapse pattern (Adeberg's classification, $p = 0.197$), although higher rates of contralateral relapses were observed in SVZ-contacting lesions versus noncontacting lesions (23.4% vs 9.1%, $p = 0.048$) (Table 3).

Discussion

This study was performed to determine the prognostic value of GB contact with the SVZ at diagnosis. On the univariate analysis, we found that patients with an SVZ-contacting tumor had significantly worse outcomes than those with non-SVZ contacting tumors for both PFS (6.1 vs. 8.7 months) and OS (10.6 vs. 17.9 months). On the multivariate analysis, this variable remained statistically significant for PFS but not OS. These data suggest that GB contact with the SVZ appears to be an independent prognostic factor for poor PFS.

These results are consistent with the findings reported by Chaichana et al. [13], who observed a lower mean OS (8 vs. 11 months, p = 0.02) in patients with SVZ-contacting tumors, and with the data reported by Jafri et al. [14], who found a lower PFS at six months and 2-year OS in patients with SVZ-contacting tumors ($p = 0.002$ in both cases).

Adeberg et al. [19] also found that direct contact or proximity (< 10 mm) between tumor and the ventricular system was significantly associated with worse prognosis. In that study, the group of patients with an OS of less than 12 months had a significantly greater percentage of lesions located in proximity to the ventricular system ($p = 0.05$) or in direct contact with the SVZ ($p = 0.05$) as compared to patients with an OS > 36 months. In addition, a meta-analysis found that patients with tumors contacting the ventricular wall had significantly worse OS and PFS outcomes as compared to patients with noncontacting tumors: with an OS of

Table 1 Patient demographics, radiological characteristics, treatment of patients

	$n = 133$
Clinical characteristic	
Median age at surgery in years (range)	63 (30–78)
Sex	84 (63%)
Male	49 (34%)
Female	
Extent of resection	62 (47%)
Biopsy	59 (44%)
STR	12 (9%)
GTR	
MGMT status	58 (44%)
Unmethylated	63 (47%)
Methylated	12 (9%)
Unknown	
KPS	80 (60%)
≤ 70	53 (40%)
> 70	
RT scheme	105 (79%)
60 Gy, 2 Gy/f	24 (18%)
40 Gy, 2.66 Gy/f	1 (1%)
55.8 Gy, 1.8 Gy/f	3 (2%)
54 Gy, 2 Gy/fr	
Concomitant TMZ uptake	7 (5%)
No	126 (95%)
Yes	
Concomitant BV	120 (90%)
No	13 (10%)
Yes	
Adjuvant TMZ	33 (25%)
No	100 (75%)
Yes	4 (1–12)
Mean cycles, *n* (range)	
Progression type ($n = 130$)	102 (78.5%)
Radiological	28 (21.5%)
Clinical	
Radiological characteristics	
Tumor location	39 (29%)
Frontal	65 (49%)
Temporal	26 (20%)
Parietal	3 (2%)
Occipital	
CC contact	121 (91%)
No	12 (9%)
Yes	
Focality at diagnosis	102 (77%)
Focal	31 (23%)
Multifocal	
SVZ contact	65 (49%)
No	68 (51%)
Yes	
Lim's classification	29 (22%)
Group 1: SVZ+, cortex+	39 (29%)
Group 2: SVZ+, cortex −	44 (33%)
Group 3: SVZ −, cortex+	21 (16%)
Group 4: SVZ −, cortex −	
Radiological characteristic at relapse	$n = 102$
Focality at relapse	43 (42%)
Focal	59 (58%)
Multifocal	

Table 1 (continued)

Radiological characteristic at relapse	$n = 102$
Adeberg's Classification	13 (13%)
IPL + Ctl	6 (6%)
IPL	39 (38%)
Local	3 (3%)
CTL	41 (40%)
Local + IPL	
Kusumawidjaja's classification (T1 weight)	83 (82%)
Central (95%)	5 (5%)
In-field (80–95%)	5 (5%)
Marginal (20–80%)	8 (8%)
Distal (> 20%)	
Adapted Kusumawidjaja's Classification (FLAIR/T2 dark fluid)	44 (44%)
Central (95%)	10 (9%)
In-field (80–95%)	36 (36%)
Marginal (20–80%)	11 (11%)
Distal (> 20%)	

STR subtotal resection, *GTR* gross total resection, *MGMT* O6-metilguanine-DNA-metiltransferase, *KPS* Karnofsky performance status, *RT* radiotherapy, *TMZ* temozolomide, *BV* bevacizumab, *SVZ* sub ventricular zone, *CC* corpus callosum, *IPL* ipsilateral, *CTL* contralateral, *n* number, *SVZ+* presence of SVZ contact, *SVZ−* absence of SVZ contact, *cortex+* presence of cortex contact, *cortex−* absence of cortex contact

12.9 vs. 16.6 months [HR 1.3 (95% CI 1.2–1.5)] and PFS of 4.5 vs. 6.3 months [HR 1.4 (95% CI 1.2–1.6)], respectively ($p < 0.0001$ in both cases) [26].

When the SVZ and cerebral cortex were both considered, we found that PFS and OS were both higher in groups 3 and 4 of Lim's classification, in which there was no contact between the tumor and the SVZ. We also observed differences between these two groups based on the presence or not of tumor contact with the cerebral cortex. The reason that group 3 presented better PFS and OS outcomes could be that the tumors were more peripheral, whereas group 4 had more central lesions located in the white matter and; thus, closer to the SVZ. However, this finding partially contradicts the data reported by Lim et al. [15] and Jafri et al. [14], who found that group 4 lesions had best prognosis. In the largest series published to date, Adeberg et al. [17] found that patients with groups 1 and 2 lesions had a lower PFS (4.8 vs. 6.9 months, $p < 0.001$) and OS (12.3 vs. 16.3 months; $p < 0.001$) compared to patients with groups 3 and 4 tumors. Possible confounding factors associated with deep tumors, which are either in direct contact with or in close proximity to the SVZ, include a greater difficulty to achieve complete resection and more involvement of deep white matter.

In our series, contact with the SVZ was an independent prognostic factor for PFS on the multivariate analysis, both when classifying patients between those with and without SVZ contact (dichotomic classification $p = 0.041$) and when considering contact with both SVZ and cerebral cortex (Lim's classification, $p = 0.047$). Our findings suggest, consistent with previous reports [27], that classifying GB lesions into SVZ-contacting or noncontacting tumors yields significant clinical associations, similar to that observed for Lim's classification method for PFS. Notably, on the multivariate analysis, none of these variables or classifications were significant for OS.

Initial anatomical contact with the SVZ was associated with a higher likelihood that the patient would present a more aggressive pattern of progression (which we denominated "clinical progression"). As our data show, this type of progression was more common in patients with SVZ-contacting tumors ($p = 0.007$), which includes groups 1 and 2 of Lim's classification ($p = 0.017$), a finding that further supports the hypothesis that these SVZ-contacting tumors have a greater potential for aggressiveness. To our knowledge, this is the first time that this association has been assessed.

We did not find any significant association between SVZ-contacting lesions and focality at diagnosis. In contrast, Lim et al. [15] and Adeberg et al. [17] both found that multifocal lesions were more common in SVZ-contacting tumors at disease onset, although Kappadakunnel et al. [28] did not find any significant correlation. On the univariate analysis performed by Lim et al. [15], both contact with the SVZ ($p = 0.004$) and the cerebral cortex ($p = 0.01$) were significantly associated with focality at diagnosis. In our series, lesions not contacting the cortex were more likely to be multifocal at diagnosis as compared to cortex-contacting tumors (35% vs. 13.7%, $p = 0.004$). Lim groups 2 and 4 were most frequently associated with multifocal presentations (35.9% and 33.3%, respectively, $p = 0.022$). This finding appears to support the theory that SVZ-contacting tumors present a more aggressive recurrence pattern, since both groups 2 and 4 included very central tumors that were, by definition, located closer to, or even in direct contact with, the SVZ. Group 1 lesions, despite contact with the SVZ, did not

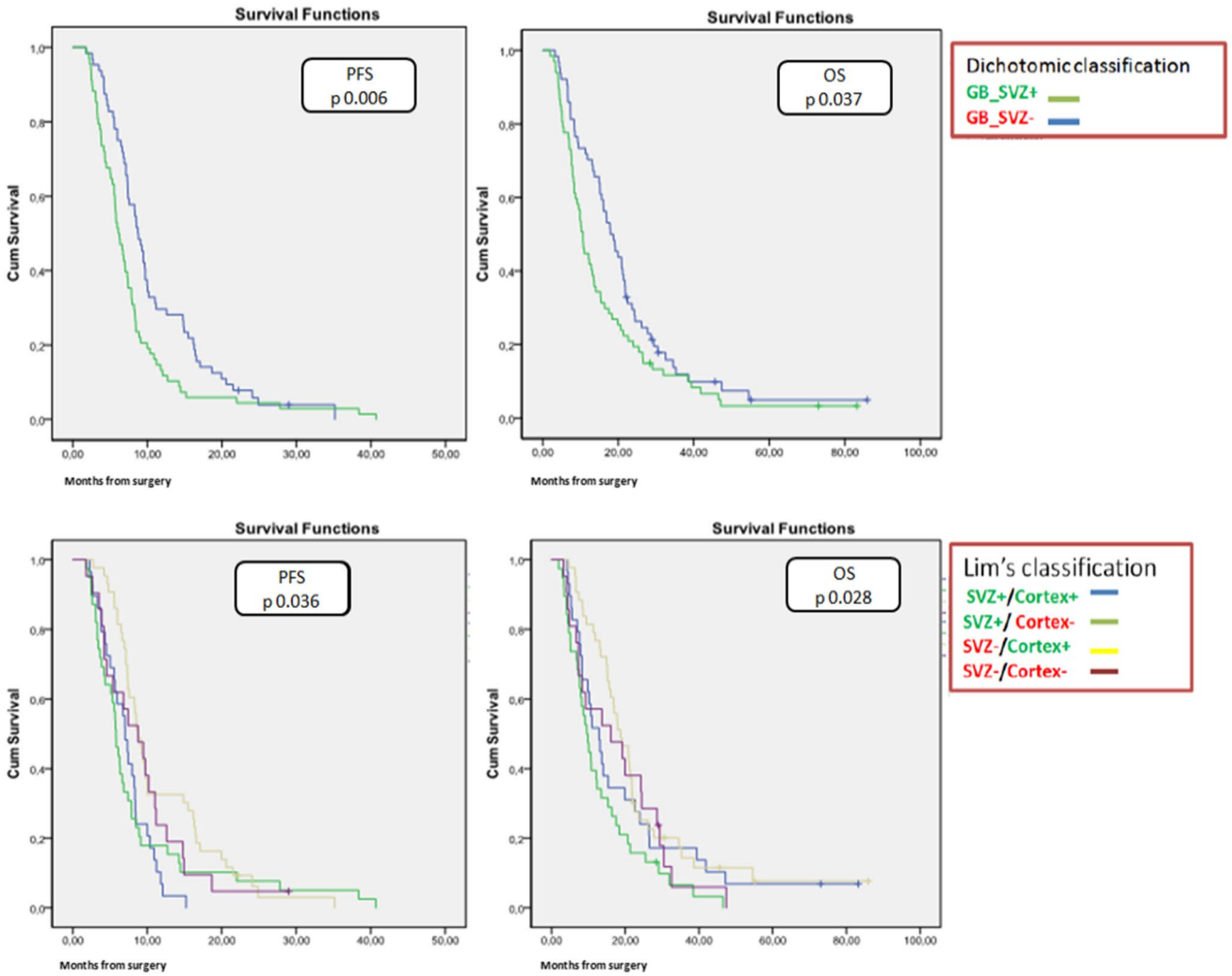

Fig. 3 Kaplan–Meier curves for PFS and OS for dichotomic classification in lesions contacting GB_SVZ+) and not contacting (GB_SVZ−) the SVZ and Lim's classification. *GB* glioblastoma, *SVZ* subventricular zone, *PFS* progression free survival, *OS* overall survival

show a high proportion of multifocal presentations, possibly because these are more extensive lesions by definition, and thus multifocality may be hidden by the extent of the injury, acting as a confounding factor.

The proportion of multifocal lesions increased considerably at relapse, rising from 23.3% at diagnosis to 57.8%. However, we were unable to find any significant association between the proximity of tumors to the SVZ or cerebral cortex and a greater probability of a focal or a multifocal relapse, although we did observe a nonsignificant trend ($p = 0.053$) towards a higher proportion of multifocal relapses in SVZ-contacting lesions.

We found a correlation between SVZ involvement and a greater proportion of distant relapses with contralateral involvement, confirming a previous report by Adeberg et al. [19], who found increased multifocal (39.8%, $p = 0.008$) and distant progressions in GB lesions in contact with the SVZ (43.8%, $p = 0.005$). Liang et al. [29] also observed an increase in contralateral relapses in these patients.

Using the classification proposed by Kusumawidjaja et al. [25], we analyzed relapses according to RT isodose lines. Of the lesions showing contrast uptake on the T1WI MRI, 81.1% were central relapses within the 95% isodose. Studies on relapse patterns have shown that most recurrences are local [30, 31], occurring within the field of irradiation in an 2 cm area around the location of the initial lesion [32–34]. Most of the patterns of progression after RT + TMZ are central, within the field of irradiation (72–93%), while relapse rates outside the irradiated area are much less frequent (2–28%) [29, 35].

Most studies conducted to date have limited the assessment of relapse patterns to the lesion visualized by contrast uptake. Nevertheless, high-grade gliomas are also composed of a component that does not take up contrast agents, that

Table 2 Multivariate survival analysis for the dichotomic classification (GB_SVZ+/GB_SVZ−) and Lim's classification

Variables		Lim's classification				Dichotomic classification (GB_SVZ+/GB_SVZ)			
		PFS HR (95% CI)	*p* value	OS HR (95% CI)	*p* value	PFS HR (95% CI)	*p* value	OS HR (95% CI)	*p* value
Lim's classification (reference category: Group 4: SVZ−/Cortex−)	Group 1: SVZ+/Cortex+	1.4 (0.7–2.7)	**0.047**	0.7 (0.3–1.3)	**0.276**				
	Group 2: SVZ+/Cortex−	1.02 (0.6–1.9)		1.2 (0.6–2.2)					
	Group 3: SVZ−/Cortex+	0.6 (0.3–1.2)		0.9 (0.5. 1.7)					
SVZ+/SVZ−						1.6 (1.02–2.5)	**0.041**	0.9 (0.6–1.4)	0.721
Type of surgery (reference category: GTR)	Biopsy	1.2 (0.6–2.6)	0.844	2 (0.9–4.4)	0.179	1.2 (0.6–2.5)	0.884	2.2 (1.04–4.7)	0.058
	STR	1.2 (0.6–2.6)		1.5 (0.7–3.2)		1.2 (0.6–2.3) 0.626		1.4 (0.7–2.9)	**(p 0.04) for Biopsy**
pMGMT methylation status		2.8 (1.9–4.2)	**< 0.001**	2.3 (1.5–3.5)	**< 0.001**	2.6 (1.8–3.9)	**< 0.001**	2.2 (1.5–3.3)	**< 0.001**
Concomitant TMZ		3.9 (1.6–9.4)	**0.003**	3.3 (1.4–7.9)	**0.007**	3.9 (1.6–9.5)	**0.002**	2.9 (1.3–6.9)	**0.013**
KPS (≤ 70 vs > 70)		1.3 (0.8–1.9)	0.267	1.2 (0.8–1.8)	0.464	1.2 (0.8–1.8)	0.313	1.1 (0.7–1.6)	0.742
Age (≤ 65 vs > 65 years)		1.3 (0.9–2.01)	0.205	2.3 (1.4–3.5)	**< 0.001**	1.5 (0.9–2.2)	0.066	2.1 (1.4–3.3)	**< 0.001**

Statistically significant results have been highlighted in bold

PFS progression free survival, *OS* overall survival, *SVZ* sub ventricular zone, *STR* subtotal resection, *GTR* gross total resection, *MGMT* O6-metilguanine-DNA-metiltransferase, *KPS* Karnofsky performance status, *TMZ* temozolomide

corresponds to subclinical infiltration and that is visible on FLAIR/T2 MRI [36]. In our sample, based on FLAIR/T2 images, there was a reduction in the number of central relapses to 43.6%, with an increase in marginal relapses, corresponding to an area between 80 and 20% of treatment isodoses. In recent years, a change in GB relapse patterns has been detected, with an increase in distal relapses[37], possibly due to the more widespread use of MRI for follow-up (which is now standard), as well the increased use of multiparametric MRI (mpMRI), and better survival outcomes due to salvage therapies.

The main limitation of this study is the retrospective design. Another limitation, similar to other published studies, is the absence of data on the isocitrate dehydrogenase (IDH) mutation. However, although some authors have described differences in the methylation status of the MGMT promoter or the IDH mutation in SVZ-contacting tumors, these differences were not statistically significant [17, 38, 39]. The main strengths of this study include the uniform treatment at a single institution and the multidisciplinary assessment by a team of experts in neuro-oncology. To our knowledge, this is the only series to date to include a hypofractionated radiation scheme (due to the inclusion of elderly or low performance status patients), who are usually excluded from such studies. Unlike most previous studies, the status of the MGMT promoter was available in most of our patients, as were the other classic prognostic factors for GB. Finally, mpMRI was used in all patients; thus, allowing for a more precise and sensitive determination of the extent of the tumors and a more accurate assessment of recurrences.

Conclusions

Our findings suggest that the presence of contact between the glioblastoma and the SVZ at diagnosis is an independent prognostic factor of faster disease progression and decreased free relapse survival. SVZ-contacting tumors were also associated with more aggressive patterns of recurrence. These findings highlight the prominent role of the SVZ in GB, revealing a clinically relevant aggressive potential for GB lesions contacting with the SVZ.

The need for prospective studies to evaluate neurogenic niches in patients with GB is essential to better understand the role that these areas play in oncogenesis and in the course of the disease. Confirmation that tumor contact with the SVZ is a prognostic factor in patients with GB would be highly valuable and would help to tailor treatments appropriately.

Table 3 Summary table of the results for focality, relapse pattern and type of progression observed for the dichotomic classification (GB_SVZ+ vs GB_SVZ−) and Lim's classification

Characteristic	*n* (%)		*p* value	*n* (%)				*p* value	Total, *n* (%)
	Dichotomic classification			Lim's classification					
	GB_SVZ+	GB_SVZ−		SVZ+/Cortex+	SVZ+/cortex-	SVZ−/cortex+	SVZ−/cortex-		
Focality at diagnosis									
Focal	52 (76.5%)	50 (76.9%)	0.951	27 (93.1%)	25 (64.1%)	36 (81.8%)	14 (66.7%)	0.022	102 (76.7%)
Multifocal	16 (23.5%)	15 (23.1%)		2 (6.9%)	14 (35.9%)	8 (18.2%)	7 (33.3%)		31 (23.3%)
					Cortex-	Cortex+			
				Focal	39 (65%)	63 (86.3%)		0.004	
				Multifocal	21 (35%)	10 (13.7%)			
Focality at relapse									
Focal	15 (31.9%)	28 (50.9%)	0.053	6 (33.4%)	9 (31%)	21 (53.8%)	7 (43.7%)	0.236	43 (42.2%)
Multifocal	32 (68.1%)	27 (49.1%)		12 (66.6%)	20 (69%)	18 (46.2%)	9 (56.3%)		59 (57.8%)
Adeberg's classification									
IPL + CTL	9 (19.1%)	4 (7.3%)	0.197	1 (5.5%)	8 (27.6%)	4 (10.2%)	0	NA	13 (12.7%)
IPL	3 (6.4%)	3 (5.4%)		2 (11.1%)	1 (3.4%)	2 (5.1%)	1 (6.3%)		6 (5.9%)
Local	13 (27.7%)	26 (47.3%)		5 (27.8%)	8 (27.6%)	19 (48.7%)	7 (43.7%)		39 (38.2%)
CTL	2 (4.2%)	1 (1.8%)		1 (5.5%)	1 (3.4%)	1 (2.6%)	0		3 (2.9%)
Local + IPL	20 (42.6%)	21 (38.2%)		9 (50%)	11 (37.9%)	13 (33.3%)	8 (50%)		41 (40.3%)
Relapse pattern									
CTL	11 (23.4%)	5 (9.1%)	0.048						16 (15.7%)
No CTL	36 (76.6%)	50 (90.9%)							86 (84.3%)
Isodose relapse (T1 weight)									
Central (95%)	38 (82.6%)	45 (81.8%)	0.511	16 (88.9%)	22 (78.6%)	32 (79.5%)	14 (87.5%)	NA	83 (81.1%)
In-field (80–95%)	1 (2.1%)	4 (7.2%)		0	1 (3.6%)	3 (7.7%)	1 (6.2%)		5 (5%)
Marginal (20–80%)	2 (4.3%)	3 (5.5%)		1 (5.5%)	1 (3.6%)	2 (5.1%)	1 (6.2%)		5 (5%)
Distal (> 20%)	5 (10.9))	3 (5.5%)		1 (5.5%)	4 (14.3%)	3 (7.7%)	0		8 (7.9%)
Adapted Isodose relapse (FLAIR/T2)									
Central (95%)	19 (41.4%)	25 (45.4%)	0.511	7 (38.9%)	12 (42.8%)	16 (41%)	9 (47.4%)	NA	44 (43.6%)
in-field (80–95%)	6 (13%)	4 (7.3%)		3 (16.7%)	3 (10.7%)	3 (7.7%)	1 (6.25%)		10 (9.9%)
Marginal (20–80%)	14 (30.4%)	22 (40%)		5 (27.8%)	9 (32.1%)	16 (41%)	6 (37.5%)		36 (35.6%)
Distal (> 20%)	7 (15.2%)	4 (7.3%)		3 (16.7%)	4 (14.3%)	4 (10.3%)	0		11 (10.9%)
Progression type									
Radiological	47 (69.1%)	55 (88.7%)	0.007	18 (62.1%)	29 (74.4%)	39 (92.9%)	16 (80%)	0.017	102 (78.5%)
Clinical	21 (30.9%)	7 (11.3%)		11 (37.9%)	10 (25.6%)	3 (7.1%)	4 (20%)		28 (21.5%)

GB_SVZ+ glioblastoma contacting SVZ, *GB_SVZ−* glioblastoma not contacting SVZ, *SVZ* sub ventricular zone, *IPL* ipsilateral, *CTL* contralateral, *n* number, *SVZ+* presence of SVZ contact, *SVZ−* absence of SVZ contact, *cortex+* presence of cortex contact, *cortex−* absence of cortex contact

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests related to the present study or manuscript.

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