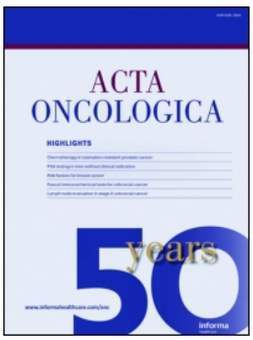

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ORIGINAL ARTICLE

Subventricular zone contacting glioblastoma: tumor size, molecular biological factors and patient survival

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ABSTRACT

Background: Several studies show that subventricular zone (SVZ) contact of glioblastoma at diagnosis is a negative prognosticator of survival. In this report, we study glioblastoma patient survival, molecular biological and MRI-based volumetric findings according to SVZ contact.

Patients and methods: We conducted a retrospective study of adult patients diagnosed with supratentorial glioblastoma and uniformly treated with temozolomide-based chemoradiotherapy after surgery. The patient cohort was dichotomized according to tumor contact with the SVZ at diagnosis as determined on preoperative MR imaging. Tumor volume was measured using semi-automated segmentation technique. MGMT-gene promoter methylation and IDH mutation status were determined on stored tumor tissue. Kaplan-Meier survival curves were constructed. Cox regression analysis was used to adjust for known confounding factors of glioblastoma patient survival.

Results: A total of 214 patients were included in the study of whom 68% belonged to the SVZ_{pos} group. Median tumor volume was significantly larger in the SVZ_{pos} group (33,8 mL vs 15,6 mL; $p < .001$). MGMT-unmethylated glioblastoma was more frequent in the SVZ_{pos} group (61.4% vs 44.9%; $p = .028$). The overall survival and progression-free survival were 12.2 months and 5.9 months for the SVZ_{pos} patient group but 16.9 months and 10.3 months for the SVZ_{neg} group (log-rank $p = .016$ and .007 respectively). In multivariate Cox survival analysis, SVZ contact proved a negative prognostic parameter, independent from age, KPS, extent of resection, MGMT-methylation and IDH mutation status.

Conclusions: This study confirms SVZ contact at diagnosis as an independent negative prognostic factor for glioblastoma patient survival. SVZ_{pos} glioblastoma had larger tumor size and a larger proportion of unmethylated tumors than SVZ_{neg} glioblastoma. Further research is needed to establish whether the observed differences are solely explained by a different molecular profile of SVZ_{pos} glioblastoma or by interaction of glioblastoma with the unique SVZ microenvironment.

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Introduction

Glioblastoma is both the most frequent and most malignant primary brain tumor in adults. Almost all patients succumb to the disease, as reflected in a five-year survival rate of only 4.6% [1]. This tumor typically presents on MR imaging of the brain as an irregularly ring-shaped zone of contrast-enhancement with central necrosis and surrounded by edema. If the contrast-enhancing part of the tumor abuts the subventricular zone (SVZ) at diagnosis, the tumor is considered as SVZ-contacting glioblastoma (SVZ_{pos}; Figure 1). In recent years, the SVZ has regained attention as the potential source of brain tumor initiating cells (BTICs), a hypothesis already formulated in 1944 by Globus and Kuhlenbeck [2]. The evidence supporting the presence of BTICs in the SVZ is now rapidly growing and these cells probably originate from neural progenitor cells (NPCs) [3–5]. Several retrospective studies acknowledge SVZ contact at diagnosis as a negative prognostic factor in glioblastoma [6–9]. The negative influence of SVZ contact of glioblastoma seems to be independent from known prognostic factors such as age, Karnofsky Performance Score (KPS), extent of resection and molecular biological factors, specifically methylation of the *0^6-methylguanine-DNA-methyltransferase* (MGMT)-promoter and *isocitrate dehydrogenase* (IDH)-mutation status [7–9]. In this report, we conducted a retrospective study of a cohort of uniformly treated *de novo* glioblastoma patients with regard to survival and demographic, MRI-based volumetric and molecular biological differences between SVZ contact groups. The prognostic significance of SVZ contact was tested both in univariate and multivariate survival analysis, adjusting for independently validated prognosticators of glioblastoma patient survival [10].

Patients & methods

Patient selection

We performed a retrospective analysis of adult (18 years or older) patients treated for supratentorial glioblastoma in two

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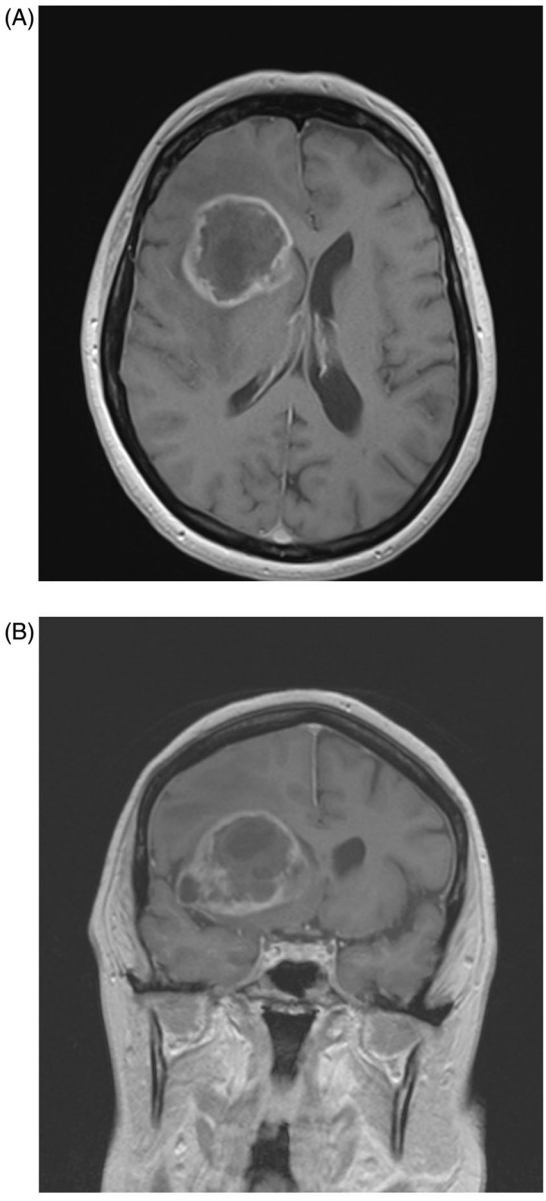

Figure 1. Contrast-enhanced axial T1 MR image (A) and matching coronal T1 image (B) illustrating a right frontal glioblastoma with SVZ contact.

hospitals in Flanders (Belgium) between 2003 and 2014. Patients were included only if they completed temozolomide-based chemoradiotherapy (60 Gy in 30 fractions) after surgery. Patients with a previous history of low-grade glioma or other brain tumors were excluded. If the preoperative imaging could not be retrieved, these patients were also excluded.

The following demographic parameters were collected from the written or electronic medical files: sex; age at diagnosis; Karnofsky performance score (KPS). Surgery was classified into biopsy only or resection, based on surgical intent. Resection was classified into subtotal resection (STR) or gross total resection (GTR) based on postoperative imaging, according to the method applied by Stummer et al. [11]. Briefly, if postoperative imaging showed the presence of contrast-enhancement of the size of one voxel or more, then surgery was classified as STR; if not, GTR was accepted. Overall survival (OS) was determined as the time between the date of histological diagnosis and the date of death. Progression-free survival (PFS) endpoint was determined by either the date of radiologic evidence of disease recurrence or progression or the date of change in treatment plan due to clinical disease progression. Patients who were still alive at the time of analysis were censored for OS. Patients without disease progression were censored for PFS at the time of the last registered follow-up visit.

This study was approved by the Ethics Committee of both participating hospitals (Belgian Registration number B670201730765; UZG 2016/1594; AZD 17004). Since the vast majority of patients had deceased at the time of analysis, the need for individual informed consent was waived by both committees.

Imaging and molecular biological factors

Contact of the contrast-enhancing part of the tumor with the SVZ was evaluated on preoperative MR imaging (SVZ_{pos} vs SVZ_{neg}). Preoperative tumor volume was measured on 3 D-T1 magnetization-prepared rapid acquisition gradient echo (MPRAGE) images with a slice thickness of 0.9 mm obtained for neuronavigation and using semi-automated segmentation technique [12]. These images were acquired on 1,5 T or 3 T magnetic resonance imaging systems (Siemens, Erlangen, Germany).

The neuropathologist selected a representative formalin-fixed paraffin-embedded tissue block from the tumor tissue archive for each case. All samples were reviewed and tested for IDH-1 and −2 mutation using next-generation sequencing techniques. MGMT promoter methylation was determined using semi-quantitative methylation-specific polymerase chain reaction (qMSP), as previously described [13].

Statistical analysis

Fisher's exact test was used to compare proportions between independent categorical variables of SVZ_{pos} and SVZ_{neg} groups and the independent samples *t*-test was applied for numerical variables, except for preoperative tumor volume. Mean difference in preoperative tumor volume between groups was assessed using a linear regression model, after log-transformation to improve normality of the measured tumor volumes. Kaplan-Meier survival curves for OS and PFS were plotted and compared between groups with the log-rank test; hazard ratios were also calculated using a univariate cox regression model. Next, a multivariate Cox regression model was fitted for survival analysis (OS and PFS), including known prognostic factors of survival in glioblastoma patients (age at diagnosis; KPS; biopsy vs resection; MGMT- methylation; IDH-mutation). In Cox regression models, numerical variables were not categorized [14]. Graphical methods were used to assess that the proportional hazards assumption was respected in Cox models for categorical variables. For numeric variables, a time-dependent covariable was introduced in the model and checked that it was not significant. All statistical analyses were performed using SPPS (v26, IBM,

Armonk, NY, USA). Statistical significance was set at $p < .05$ using two-tailed tests.

Results

In total, 399 patients were surgically treated for glioblastoma. Three patients were excluded because of cerebellar localization or the presence of other tumors; 43 were lost to follow-up; 93 patients were treated with shortened radiotherapy schedules or without temozolomide; diagnostic MR imaging could not be retrieved in 46 patients. So, 214 patients were included in the study of whom 12 were still alive at the time of database closure. The majority of patients (68%) belonged to the SVZ_{pos} group (Table 1). IDH mutation could not be determined due to technical reasons in 19.5% of patients while MGMT-methylation status is lacking in 8% of patients. Only the $IDH1^{R132}$ mutation was found. The difference in tumor size and in MGMT-methylation status between SVZ contact groups proved statistically significant (Table 1). The number of unmethylated tumors was higher in the SVZ_{pos} group while in the SVZ_{neg} group the numbers of methylated and unmethylated tumors were proportionally distributed (44.9% unmethylated and 46.4% methylated; Table 1). There was no difference in frequency of IDH-mutation between SVZ contact groups. Tumor volume could be determined in 177 patients. Median tumor volume was more than double in the SVZ_{pos} glioblastoma group (33.8 mL for SVZ_{pos} vs 15.6 mL for SVZ_{neg}; $p < .001$). There were no significant differences in age, KPS, female/male ratio or extent of surgical resection between SVZ contact groups.

Univariate survival analysis showed that age, KPS, extent of resection, MGMT-methylation status and IDH-mutation correlated significantly with glioblastoma patient survival albeit IDH-mutation only for PFS (Table 2). Preoperative tumor volume did not correlate with survival in univariate Cox regression model. SVZ contact was a significant prognostic factor for both OS (SVZ_{pos} median OS 12.2 months vs SVZ_{neg} median OS 16.9 months; $p = .016$) and PFS (SVZ_{pos} median PFS 5.9 vs SVZ_{neg} median PFS 10.3 months; $p = .007$). After adjustment for age, KPS, surgical resection, IDH-mutation and MGMT-methylation status, SVZ contact proved a statistically significant prognostic factor both for OS and PFS (Table 3, Figure 2).

Discussion

This study confirms SVZ contact as an independent negative prognostic factor in glioblastoma patient survival. Compared to SVZ_{neg} tumors, SVZ_{pos} glioblastoma has a double median tumor volume and comprises predominantly MGMT-unmethylated tumors. There were no significant differences between SVZ contact groups with regard to sex ratio, age, KPS, extent of resection or IDH-mutation.

Contrary to our results, a recent meta-analysis of 6 reports on MGMT-methylation status of SVZ_{pos} glioblastoma, showed no significant difference between SVZ contact groups concerning this important prognostic epigenetic factor [15]. This was also the case in the prospective study on SVZ contacting glioblastoma by Van Dijken et al. [7]. However, a 2018 report by Han et al. on predicting MGMT promoter methylation status based on preoperative MR imaging, showed similar results to this study, with a significantly higher number of unmethylated tumors in the SVZ_{pos} group compared to the SVZ_{neg} group (58.3% vs 36.4% resp.; $p = .012$) [16]. Literature does not allow to draw a definitive conclusion at present whether SVZ_{pos} glioblastoma has a different MGMT-methylation pattern than SVZ_{neg} tumors.

Importantly, despite the obvious higher number of unmethylated tumors in the SVZ_{pos} group, SVZ contact was an independent prognostic factor in multivariate survival

Table 1. Overview of demographic, surgical, molecular biological and volumetric characteristics as well as survival according to subventricular zone contact group.

Parameter	SVZ contact	No SVZ contact	*p*-value
N (%)	145 (68%)	69 (32%)	–
Sex			.223[a]
Female	55 (38%)	20 (29%)	
Male	90 (62%)	49 (71%)	
Mean age at diagnosis (years)	60	62	.162[b]
KPS (mean)	70	70	.115[b]
Surgery			.552[a]
Biopsy only	40 (27.6%)	15 (21.7%)	
STR	60 (41.4%)	28 (40.6%)	
GTR	45 (31.0%)	26 (37.7%)	
MGMT-methylation			**.028**[c]
No	89 (61.4%)	31 (44.9%)	
Yes	45 (31%)	32 (46.4%)	
unknown	11 (7.6%)	6 (8.7%)	
IDH-mutation			.276[c]
No	111 (76.6%)	44 (63.8%)	
Yes	10 (6.9%)	7 (10.1%)	
unknown	24 (16.5%)	18 (26.1%)	
Median tumor volume (mL)*	33.8	15.6	**<.001**[d]
Median overall survival (months)	12.2	16.9	**.016**[e]
Median progression-free survival (months)	5.9	10.3	**.007**[e]

[a]Fisher's exact test. [b]Independent samples *t*-test. [c]Fisher's exact test with exclusion of *NA* group. [d]Linear regression model of the log transformed volumes. [e]Log-rank test. *Available in 177 patients.
Significant *p*-values are highlighted in bold. KPS = Karnofsky Performance Score; STR = subtotal resection; GTR = gross total resection; MGMT = 0^6-methylguanine-DNA-methyltransferase; IDH = isocitrate dehydrogenase.

Table 2. Univariate survival analysis for several prognostic factors of glioblastoma patient survival.

		Overall survival			Progression-free survival		
Parameter	% of patients	Median (months)	Hazard ratio (95% CI)	Wald test *p*	Median (months)	Hazard ratio (95% CI)	Wald test *p*
Age at diagnosis (years)							
≥65	35,5%	11.7	1.021 (1.009–1.034)*	**.001**	6.2	1.009 (0.997–1.021)*	.161
<65	64,5%	14.3			6.7		
KPS							
≥70	70%	15.33	0.981 (0.971–0.991)*	**<.001**	7.7	0.987 (0.978–0.997)*	**.010**
<70	30%	9.4			4.6		
Preoperative tumor volume*	82.7%	–	0.997 (0.985–1.009	.588	–	1.005 (0.992–1.019)	.469
Surgery							
Biopsy only	25,7%	8.7	–	–	4.7		
STR	41,1%	13.0	0.673 (0.480–0.944)	**.022**	6.2	0.589 (0.417–0.832)	**.003**
GTR	33,2%	17.0	0.503 (0.371–0.682)	**<.001**	10.7	0.554 (0.403–0.760)	**<.001**
MGMT-methylation							
Yes	39%	20.9	0.361 (0.263–0.497)	**<.001**	12.0	0.471 (0.343–0.649)	**<.001**
No	61%	11.5			5.5		
IDH-mutation							
Yes	10%	23.8	0.612 (0.359–1.044)	.072	11.3	0.548 (0.319–0.939)	**.029**
No	90%	13.4			6.3		
SVZ contact							
Yes	68%	12.2	1.439 (1.067–1.941)	**.017**	5.9	1.523 (1.119–2.072)	**.007**
No	32%	16.9			10.3		

*Numerical variables were not categorized in Cox regression model.
Significant *p*-values are highlighted in bold. KPS = Karnofsky Performance Score; STR = subtotal resection; GTR = gross total resection; MGMT = 0^6-methylguanine-DNA-methyltransferase; IDH = isocitrate dehydrogenase; SVZ = subventricular zone.

Table 3. Multivariate Cox regression model of glioblastoma patient survival adjusted for age, KPS, extent of resection, MGMT-methylation and SVZ contact.

Parameter	Overall survival hazard ratio (95% CI)	Wald test *p*	Progression-free survival hazard ratio (95% CI)	Wald test *p*
Age	1.029 (1.014–1.045)	**<.001**	1.013 (0.998–1.028)	.093
KPS	0.982 (0.969–0.995)	**.008**	0.985 (0.973–0.997)	**.018**
Biopsy vs resection	0.503 (0.343–0.736)	**<.001**	0.594 (0.405–0.872)	**.008**
MGMT-methylated	0.294 (0.203–0.425)	**<.001**	0.442 (0.308–0.634)	**<.001**
IDH-mutated	0.685 (0.518–1.541)	.685	0.653 (0.368–1.158)	.145
With SVZ contact	1.464 (1.027–2.088)	**.035**	1.483 (1.037–2.121)	**.031**

Significant *p*-values are highlighted in bold. CI = confidence interval; KPS = Karnofsky Performance Score; MGMT = 0^6-methylguanine-DNA-methyltransferase; IDH = isocitrate dehydrogenase; SVZ = subventricular zone.

analysis. Our survival results are analogous to the results of the 2017 meta-analysis on SVZ contact and glioblastoma patient survival [6] and to those more recently obtained by Van Dijken et al. [7] and Mistry et al. [9]. In their 2019 study, Mistry et al. showed that SVZ_{pos} glioblastoma was associated with decreased survival and also with post-treatment hydrocephalus and leptomeningeal dissemination. This negative influence on glioblastoma patient survival of SVZ contact was also independent from ventricular entry during neurosurgical resection [9]. Moreover, in another report studying TCGA molecular data of glioblastoma, the same group could not find a distinct molecular biological profile of SVZ_{pos} glioblastoma [17]. Another group came to the same findings [8]. If the molecular signature of SVZ_{pos} tumors is not fundamentally different from SVZ_{neg} glioblastoma, possibly the interplay between glioblastoma cells and the complex and unique SVZ niche may hold the key to understanding how SVZ contact of glioblastoma influences patient survival [18]. For example, it has been shown in a mouse model that glioma cells invading the SVZ become radioresistant by influence of SVZ chemokines [19].

The current finding of significantly larger tumor size for SVZ_{pos} glioblastoma is consistent with previously published findings [7,8,15,20]. Nevertheless, this observation alone is insufficient to establish the SVZ origin of glioblastoma. A direct correlation between anatomical localization of glioblastoma and its origin is unlikely [20]. Mathematical glioma growth models demonstrate that tumors originating at a distance from the SVZ have a high likelihood of reaching the SVZ before detection [21,22]. SVZ_{pos} glioblastoma may just be the consequence of a highly malignant and rapidly growing tumoral lesion within the limited confinements of the brain rather than the indication of pure SVZ origin [22].

Most importantly, this study acknowledges SVZ contact as a negative prognostic factor for glioblastoma patient survival, independent from age, KPS, extent of resection, MGMT-methylation status and IDH mutation (Table 3, Figure 2). In other words, SVZ_{pos} glioblastoma is even more aggressive than SVZ_{neg} tumors. The SVZ niche in glioblastoma patients may become a therapeutic target in the future whether by radiating the SVZ or by targeting specific components of the SVZ microenvironment [5,18]. We join the call already made by Smith et al. in 2016 to increase translational and basic research on the SVZ and its role in glioblastoma [23].

This study has several shortcomings of which selection bias due to the retrospective study design may be the most important. Furthermore, corticosteroid use at diagnosis was not included in the analysis nor were the different treatment

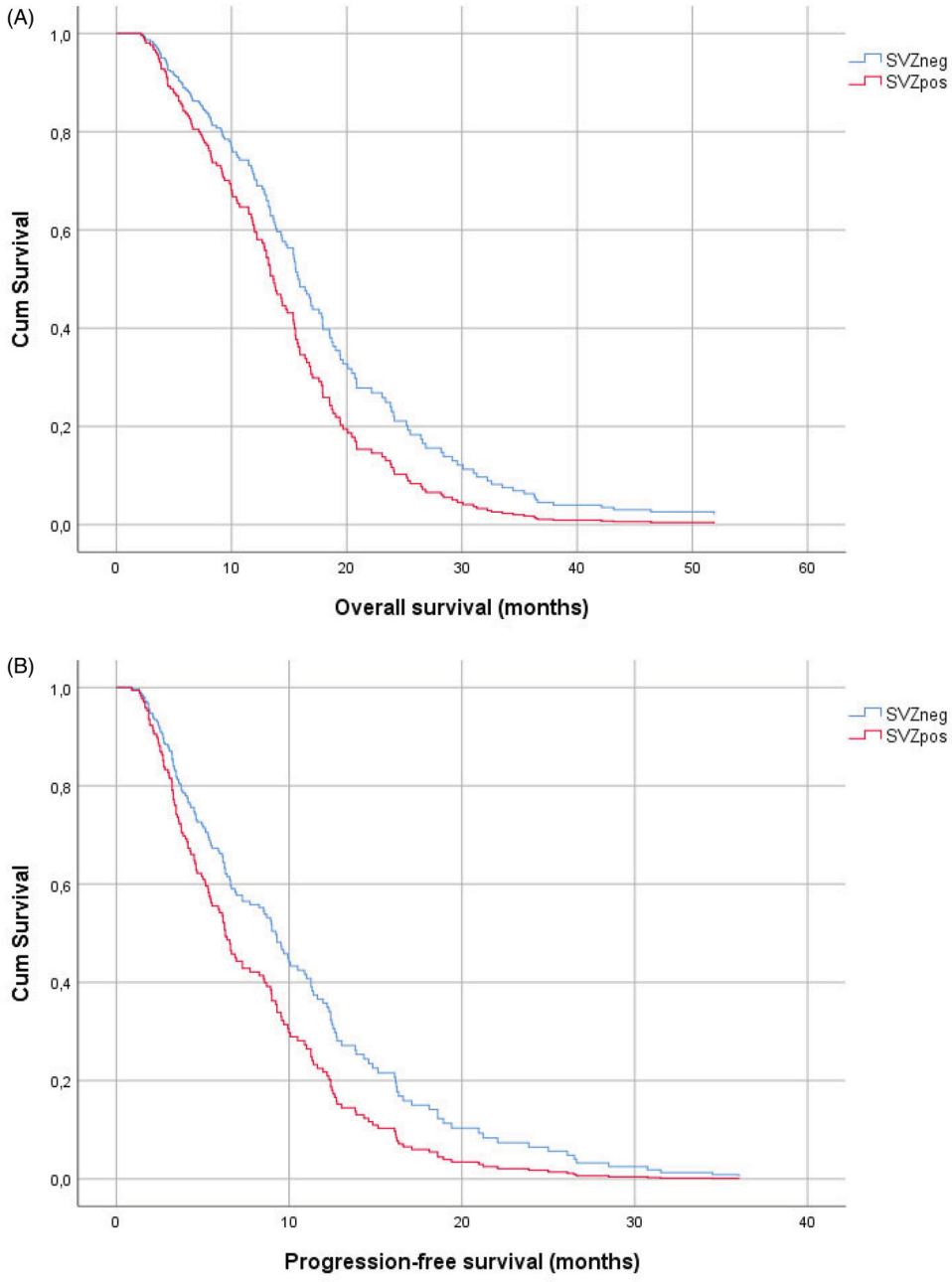

Figure 2. Kaplan-Meier curves of overall survival (A) and progression-free survival (B) in glioblastoma with (SVZ_{pos}) and without (SVZ_{neg}) subventricular zone contact.

modalities applied for disease recurrence or progression. Nevertheless, we present a large series of glioblastoma patients who were uniformly treated in first tier treatment. We were able to include MGMT-promoter methylation status and IDH-mutation in the study and adjust survival analysis for these and other well-known prognostic factors.

Conclusion

In this glioblastoma patient cohort, SVZ contact at diagnosis is a negative and independent prognostic factor. The SVZ_{pos} patient group had significantly more MGMT-unmethylated and larger tumors. More studies are needed to be able to draw a definitive conclusion whether differences in MGMT-methylation pattern exist between glioblastoma SVZ contact groups. The role of SVZ contact in glioblastoma needs to be examined further in larger patient groups in order to establish how SVZ contact influences patient survival. The SVZ emerges as a potential therapeutic target in glioblastoma treatment.

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Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or

national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the ethics committee of both participating hospitals (Belgian Registration number B670201730765; AZD 17004; UZG 2016/1594).

Informed consent

The need for informed consent was waived by the ethical committees of both participating hospitals.

Author contributions

All authors contributed to the study conception and design. Material preparation and data collection and analysis were performed by Giorgio Hallaert and Harry Pinson. The first draft of the manuscript was written by Giorgio Hallaert and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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