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Research Article

Periventricular zone involvement as a predictor of survival in glioblastoma patients: A single centre cohort-comparison investigation concerning a distinct clinical entity

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ABSTRACT

Background: Glioblastoma (GBM) contacting the Subventricular Zone (SVZ) may display a more aggressive pattern of invasiveness with higher potential to recruit migratory progenitor cells. We aims to determine the relationships between the location of the lesion and the clinical, molecular characteristics and outcome in patients affected by GBM.

Methods: The surgical, radiological and clinical outcomes of patients have been retrospectively reviewed for the present study. All patients have been classified according their anatomical relationship with SVZ in SVZ + and SVZ-. A review of our surgical series was conducted to compare the results of SVZ tumors in regards to clinical and molecular characteristics, localization, and Extent of Resection (EOR). Uni- and Multivariate ANOVA and survival analyses were performed to investigate the cohort.

Results: A total of 177 patients were included in the final cohort. A statistical analysis by means of multivariate analyses to demonstrate that SVZ + tumors were significantly associated to a greater volume at presentation, a lesser EOR, lesser functional postoperative outcome and a short overall survival.

Conclusions: There are specific characteristics to consider the SVZ + GBMs a specific clinical entity how greater tumors at presentation, clinical associated with Headache and Sensory Disturbances, which are associated to a higher risk of partial resection and with a less satisfactory functional outcome in the early postoperative period. Our multivariate analysis demonstrated a clear and statistically significant survival advantage of cortical GBM over V-SVZ GBM.

1. Introduction

The diagnosis of Glioblastoma (GB) is still burdened by an overall poor oncologic prognosis with high morbidity and mortality [1,2,8]. It was argued that a GB contacting the Subventricular Zone (SVZ) may display a more aggressive pattern of invasiveness with higher potential to recruit migratory progenitor cells [4,5,8]. Moreover some authors assessed a possible predictive role of the topographic location of the lesion in regards to their biological signatures and clinical outcomes [18]. Ventricular or periventricular GBs involving the ventricular-subventricular zone (V-SVZ), could represent a special subcohort of High grade Gliomas with unique features [1–5,7,8]. The SVZ is a known

Abbreviations: **SVZ**, Subventricular Zone; **V-SVZ**, Ventricular Subventricular Zone; **DTI**, Diffusion Tensor Imaging; **DWI**, Diffusion Weighted Imaging; **EGFR**, Epidermal Growth Factor Receptor; **EOR**, Extent Of Resection; **FLAIR**, Fluid Attenuated Inversion recovery; **fMRI**, Functional Magnetic Resonance Imaging; **GBM**, Glioblastoma; **GTR**, Gross Total Resection; **HGG**, High Grade Gliomas; IDH, Isocitrate Dehydrogenase; **IoN**, Intraoperative Neurophysiological monitoring; **IoNT**, Intraoperative Neuropsicological testing; **LGG**, Low Grade Gliomas; KPS, Karnofsky Performance Status; **MPRAGE**, Magnetization-Prepared Rapid Gradient-Echo; MRI, Magnetic Resonance Imaging; **NTR**, Near Total Resection; **STR**, Subtotal Resection; **OS**, Overall Survival; **PFS**, Progression Free Survival; QoL, Quality of Life; **NSC**, Neural Stem Cells; **BTPC**, Brain Tumor Proliferating Cells.

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neurogenic niche harboring neural stem and progenitor cells (NSC). Whether radiographic contact with the LV influences survival in GB patients remains unclear [14]. Our purpose is to investigate the relationships between the location of the lesion and the molecular characteristics and the survival in patients affected by GB in a collection of 177 patients divided in SVZ + GB (that contacting or involve the ventricles) and SVZ- GB.

1.1. Purpose of the present investigation

Our specific aim was to determine whether the SVZ involvement (Fig. 1) in GBs is associated with a higher recurrence rate and a shorter Overall Survival (OS) and Progression Free Survival (PFS), analyzing tumor volume, immunohistochemistry patterns, functional and neurological outcomes. MR imaging and clinical data from 177 patients with GBM treated at our institution were retrospectively reviewed in order to investigate this extremely precise topic.

2. Material and methods

2.1. Participants and eligibility

We performed an Institutional retrospective review of a consecutive series of surgically-treated patients suffering from histologically confirmed GB, operated on in our department. We collected a total of 193 patients suffering from GB. Histological diagnoses were performed according to the updated version of the WHO guidelines [24].

We selected a total of 177 patients affected by newly diagnosed GB who underwent at their first surgery, radiation, and chemotherapy in our Institution in the period ranging between January 2014 and December 2016 meeting the following inclusion criteria:

- 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.
- Patients were included if, in the postoperative period, could undergo a standard STUPP protocol starting from the 30th-35th day after surgery.
- Patients were included if they received a standard conformational planning with a Linear Accelerator (LINAC), no stereotactic radiosurgical treatment was performed.
- The estimated target of the surgical procedure was the *total or subtotal resection of the lesions*: no biopsies were included.

16 patients were excluded for incomplete or wrong data on clinical, radiological and surgical records and/or lost to follow-up (Fig. 2).

All the patients who met the aforementioned inclusion criteria, were assigned on the ground of the preoperative imaging to the following subgroups:

- Tumors classified as SVZ+: The contrast-enhancing lesion contacts the SVZ wall or involves the ventricles (81 patients).
- Tumors classified as SVZ-: The contrast-enhancing lesion does not contact the SVZ (96 patients).

We identified the GBM-SVZ if the contrast enhancing is within a 5 mm margin surrounding the ventricles corresponding to earlier definitions of the SVZ used by other authors [33–35].

We investigated whether the presence or absence of an anatomical relationship between tumor and SVZ (SVZ + GB/SVZ- GB) supports the hypothesis of cancer arising from stem or progenitor cell population [11,13] and is indicative how different OS or molecular characteristic

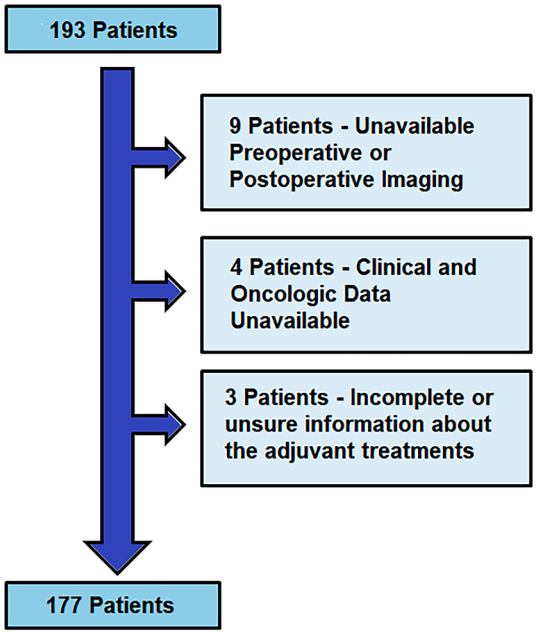

Fig. 2. Flow Chart depicting the excluded patients.

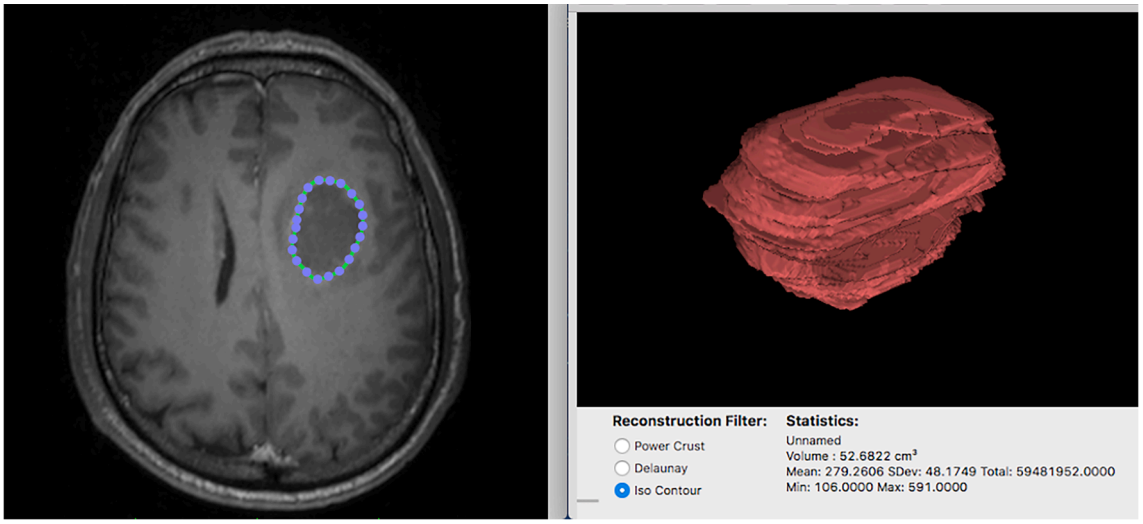

Fig. 1. A typical SVZ + tumor, disclosing an extensive contact interface with the Subventricular Zone, measured with a Osirix Software system [26].

since current evidence is still limited by incomplete study designs and inconsistent survival outcomes, an undisputed definition of "SVZ area".

For all the included patients we recorded age, sex, location, Tumor volumen, clinical onset, IDH, Ki67, p53 and EGFR expression status. In particular, the specimens used in this study were examined for IDH mutation. Immunohistochemistry with ki67, EGFR, ATRX and antibody anti-IDH1 R132H (Dianova, DIA H09; 1:50) was routinely performed in the Department of Neuropathology of our Hospital. A MGMT methylation status analysis was realized by means of a Real Time PCR test, and the results were available in a total of 53/177 patients. OS was recorded in months; it was measured from date of diagnosis to date of death or date of last contact if alive. Clinical information were obtained by the digital database of our Institution, whereas OS data, were obtained by telephone-interview. A special focus was on the KPS results: such parameter was considered, as previously observed [25] as predictive and associated to survival. In particular it was recorded in three different moments: 1. Before surgery, 2. At 30 day after surgery and 3. At the end of the adjuvant treatment (the moment of the last outpatient evaluation).

All the patients included underwent a preoperative brain MRI scan included an high field 3 Tesla volumetric study with the following sequences: T2w, FLAIR, isotropic volumetric T1-weighted magnetization-prepared rapid acquisition gradient echo (MPRAGE) before and after intravenous administration of paramagnetic contrast agent; diffusion tensor sequences (DTI) with 3D tractography and functional MRI (fMRI) completed our protocol for what concerns gliomas affecting eloquent locations [7,8,43]. Volume of the contrast-enhancing lesion was calculated drawing a region of interest (ROI) in a Volumetric enhancing post-contrast study weighted in T1 (a multi-voxel study), conforming to the margins of the contrast- enhancing lesion with software Osirix [26]. In the first postoperative day, the patients underwent volumetric Brain MRI scan to evaluate the EOR.

For both subgroups (Patients suffering from SVZ + and SVZ- tumors), in case of non-eloquently located lesion, a standard total intravenous anesthesia protocol with Propofol (1 mg/kg) and Remifentanil (0,5 μg/kg/min) has been used. For lesions involving the motor cortices and language related functional cortices, a standard Full Awake Surgery protocol was routinely performed [40,42] with the aid of Intraoperative Neuromonitoring realized with use of bi- and monopolar stimulating probes respectively for the cortical and subcortical mapping.

In general, it was intraoperatively judged necessary to stop tumor excision when:

1. white matter appeared free of disease in any aspect of the surgical cavity,
2. despite a directly visualized or a Navigation proven remnant, neuromonitoring or intraoperative neuropsychological testing outlined a risk for postoperative motor morbidity, [37–39].

2.2. Data sources and quantitative variables

The extent of resection (EOR) was determined through a comparison between the MR images obtained before surgery and the first early MRI after surgery. EOR was calculated as a percentage by comparing the preoperative and early postoperative imaging, with the aforementioned software. Gross Total Resection (GTR), was defined as resection without visual residual enhancing tumor confirmed by Flair and T1 with contrast sequences, conversely a Near or Subtotal Resection was the surgical result on radicality (NTR/STR).

In the case of GTR, "tumor progression" was defined as the first MRI scan compatible with "tumor progression" according to the RANO criteria and the first MRI scan demonstrating the presence of pathologically enhancing tissue characterized by an MRI pattern (relying mostly on Perfusion Weighted Imaging) inconsistent with a cerebral radiation injury. In case of incomplete resections (<95% volume reduction), the same compliance to RANO criteria was adopted as standard, furthermore a volumetric increase of the residual disease detected at the first postoperative MRI scan, if enhanced in PWI, was considered as disease progression, thus obtaining the time to progression or Progression-Free Survival (PFS).

A close range dedicated neuro-imaging follow-up program (composed by both a CT scan [43] in a first post-surgical day and a brain MRI scan) was routinely performed in our Institution for every patients included in this study. This program included:

A standard early (maximum 24 h after surgery) postoperative volumetric brain MRI.

At approximately one month from surgery (25–35 days) a volumetric brain MRI scan was repeated for a first step follow-up control and to provide information for the radiation treatment planning [40,41].

After the end of irradiation, a volumetric brain MRI scan was performed every three months [41].

Generally the treatment was considered to be stopped when disease showed volumetric progression despite the second line of adjuvant treatment [42]. Both subgroups received a surgical and adjuvant treatment with *The same operative microscope, Similar infrared-based Neuronavigation system, Similar microsurgical instruments, the same adjuvant treatment and follow-up program.*

2.3. Statistical methods

The sample was analyzed with SPSS version 18. Comparison between nominal variables have been made with Chi^2 test. EOR and PFS means were compared with One Way and Multivariate ANOVA analysis along with Contrast analysis and Post-Hoc Tests. Cox Regression Model survival analysis assessed survival. Continuous variables correlations have been investigated with Pearson's Bivariate correlation. Threshold of statistical significance was considered $p < 0.05$.

2.4. Potential source of bias and study size

We addressed no missing data since incomplete records were an exclusion criteria. A potential source of bias is expected to derive from exiguity of the sample, which nevertheless, in regards to the endpoints selected, presents an excellent post-hoc statistical estimated power (difference between two independent means; $1\text{-}\beta = 0.9488$ for α 0.05 and effect size 0.5), thus providing extremely reliable conclusions.

The informed consent were approved by the Institutional Review Board of our Institution. Before surgical procedure, all the patients gave informed written explicit consent after appropriate information. Data reported in the study have been completely anonymized. No treatment randomization has been performed. This study is perfectly consistent with Helsinki declaration of Ethical principles for medical research to humans.

3. Results

3.1. Participants

In the period between between January 2014 and December 2016, 177 patients, matching the inclusion criteria, suffering from GB underwent surgery in our department and were retrospectively evaluated for this study.

3.2. Descriptive data

The final cohort consisted of 97 males and 80 females, and the average age was 60.93 ± 12.76 years (Range 23–84); In a final division in a main subgroup SVZ lesions were 81 (45.7%) and no contacting the SVZ were 96. 55 tumors (31.1%) were purely frontal, 34 (19.2%) in temporal lobe, 16 (9.0%) in parietal lobe, 4 (2.3%) in occipital lobe; Insula, Rolandic area and Corpus Callosum were respectively involved in a total of 13 (7.8%), 9(5.4%) and 5 (1.8%) patients. A total of 78 tumors

were located on the left hemisphere. All the relevant details are included in Table 1.

The two subgroups presented remarkable differences from the clinical point of view: it was possible to retrieve a trend to higher incidence of Headache (19/81 versus 14/96 – 23.46% versus 14.58%), lower incidence Seizures (16/81 versus 33/96 – 19.75% versus 34.38%) and higher incidence of Sensory Disturbances (29/81 versus 21/96 – 35.80% versus 21.81%) in the SVZ + tumors group (respectively p = 0.053; 0.070 and 0.013). Conversely, from the histochemical point of view the two subgroups did not show relevant differences in concerns to the expression of the IDH mutation, EGFR and Ki67 overespression, p53 mutation (Details in Table 1). In our study MGMT methylation status in 53 out of 177 demonstrated a higher incidence in SVZ + tumor patients (p = 019). For a total of 124 patients, MGMT methylation pattern was investigated in a different Institution, and the relevant data are not available.

Concerning the preoperative volume of the lesions showed a statistically significant difference between the two subgroups (p = 0.001): SVZ + tumors demonstrated a strong tendency towards higher volume at presentation; EOR accordingly, favored the SVZ- tumors (GTR rate was 76.0% versus 89.77% for SVZ + and SVZ- tumors respectively – Fig. 3). This finding presents a strong statistical significance (p = 0.022). From a functional point of view, KPS of the two subgroups appeared to be perfectly matched preoperatively (83.2 ± 12.85 versus 82.9 ± 10.87; p = 0.862) and at the last evaluation (39.26 ± 17.41 versus 39.21 ± 18.13; p = 0.988), while the clear and statistically significant difference was in the KPS evaluation after surgery (KPS ≥ 80 in 60.76% versus 77.66% of patients respectively for SVZ + and SVZ- tumors subgroups; p = 0.016 – Fig. 4A and B).

Table 1
Patient's demographics.

N = 177 patients			P value
Subgroup	SVZ+ = 81	SVZ- = 96	–
Sex	Male N = 47 – 58% Female N = 34 – 42%	Male N = 50–52.1% Female N = 46; 48%	0.311
Age	61.7 years ± 12,75	60.28 ± 12,81	0.409
KPS at admission	KPS > = 80: 56/ 81–69.14% KPS < 80: 25/ 81–30.86%	KPS > = 80: 86/96 – 89.58% KPS < 80: 10/ 96–10.42%	0. 001
Volume in cm^3	31.15 ± 18.5	14.07 ± 14	0.001
Ki67 (%)	23.52 ± 13.85	25.46 ± 15.09	0.470
IDH available in 166/ 177 pts	IDH Mutant 2/81 (2,47%)	IDH Mutant 0/96	0.197
EGFR available in 149/177 pts	EGFR Overexpressed 50/71 (70.42%)	EGFR Overexpressed 56/84 (66.66%)	0.117
p53 mutation screening available in 150/177 pts	Mutant p53 39/67 (58.2%)	Mutant p53 45/84 (53.57%)	0.305
EOR	GTR 57/75 patients (76%) STR 18/75 patients (24%)	GTR 79/88 patients (89.77%) STR 9/88 patients (10.22%)	0.020
KPS after surgery	KPS > = 80: 48/ 79–60.76% KPS < 80: 31/ 79–39.24%	KPS > = 80: 73/ 94–77.66% KPS < 80: 21/ 94–22.34%	0.016
KPS at last evaluation	KPS > = 80: 5/ 77–6.5% KPS < 80: 72/ 77–93.5%	KPS > = 80: 5/ 89–5.62% KPS < 80: 84/ 89–94.38%	0.829
Overall Survival	12.07 ± 7.69 months	17.02 ± 11.06 months	0.002
PFS	5.80 ± 6.34 months	9.70 ± 9.73 months	0.005
Location	Frontal 27 (33.3%) Temporal 35 (43.21%) Occipital 4 (4.94%) Parietal 10 (12.35%) Corpus Callosum 5 (6.17%)	Frontal 31 (32.3%) Temporal 34 (35.42%) Occipital 3 (3.125%) Parietal 20 (20.83%) Corpus Callosum 8 (8.33%)	0.314
Side	Left 35 (43.2%) Right 40 (49.4%) Midline 4 (4.93%) Multifocal 2 (2.47%)	Left 44 (45.83%) Right 49 (51.04%) Midline 1 (1.04%) Multifocal 2 (2.08%)	0.471
Symptoms	Headache 19 (23.46%) Seizures 16 (19.75%) Speech Disturbance 6 (7.41%) Motor Dysfunction 3 (3.70%) Sensory Disturbance-dizziness 29 (35.8%) Visual Deficit 5 (6.17%) Incidental 3 (3.71%)	Headache 14 (14.58%) Seizures 33 (34.38%) Speech Disturbance 15 (15.63%) Motor Dysfunction 7 (7.29%) Sensory Disturbance 21 (21.81%) Visual Deficit 5 (3.4%) Incidental 1 (1.04%)	0.059 0.070 0.128 0.223 0.013 0.259 0.414

PFS: Progression Free Survival; **OS**: Overall Survival; **SVZ:** Subventricular Zone, **KPS:** Karnofsky performance status, **EOR:** Extent of Resection, **GTR:** Gross Total Resection, **NTR/STR:** Near Total/Subtotal Resection.

3.3. Outcome data and main results

The median OS was 17.02 ± 11.06 months and 12.07 ± 7.69 months respectively for SVZ- and SVZ + tumors, with a clear statistical significance (p = 0.002); similar results were outlined in regards to Progression Free Survival (5.80 ± 6.34 versus 9.70 ± 9.73 months, for SVZ + and II respectively. statistically significant; p = 0.005).

Multivariate ANOVA analysis performed on the survival variables disclosed that Volume of the Lesion in cm^3 is an independent predictor of OS by means of a statistically significant association, independently from the contact with the SVZ (Fig. 5a – p = 0.008), and similar results were disclosed in concern to PFS (p = 0.004 – Fig. 5b). Contact of the Tumor with SVZ area, proved to be in a multivariate ANOVA analysis as a predictor of shorter survival independently from the Age of the patients (p = 0.002 – Figs. 5a and b), similar, statistically significant results were identified in regards to PFS (p = 0.033). Multivariate ANOVA analyses ruled out possible statistically significant effects on survival parameters between the contact of the tumor with SVZ area with EGFR, p53, and Ki67 (p values between p = 0.217 and p = 0.734) (Fig. 6).

In regards to Cox Regression Model survival curves, SVZ- demonstrated a clear and statistically significant survival advantage over SVZ+, both in regards to PFS and OS (Fig. 7a and Fig. 7b; with *p = 0.020 and p = 0.003 respectively*), further confirming the previously reported findings. OS showed strong statistical correlations with EOR and PFS

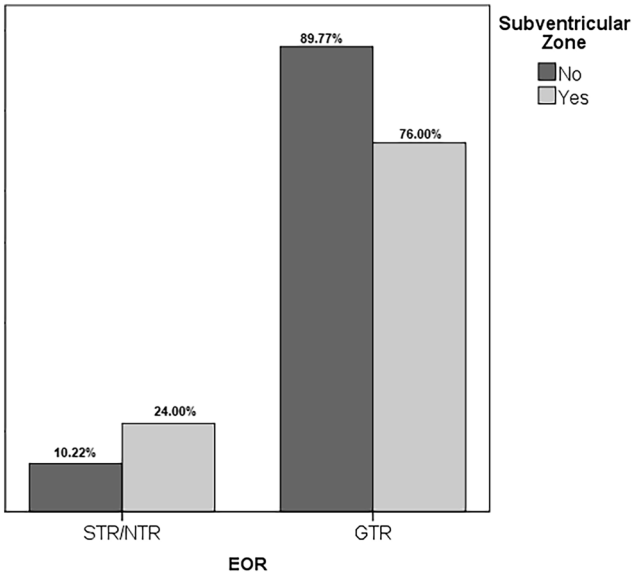

Fig. 3. Bar Charts disclosing a Chi^2 analysis concerning EOR and Subventricular Zone.

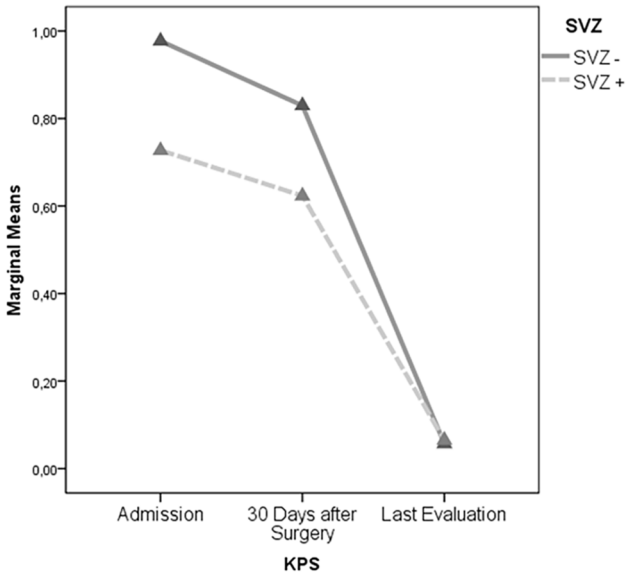

Fig. 4. A and B – A. Bar Charts disclosing a Chi^2 analysis concerning KPS at 30 days and Subventricular Zone. B. Repeated Measures ANOVA analysis disclosing the KPS Trend.

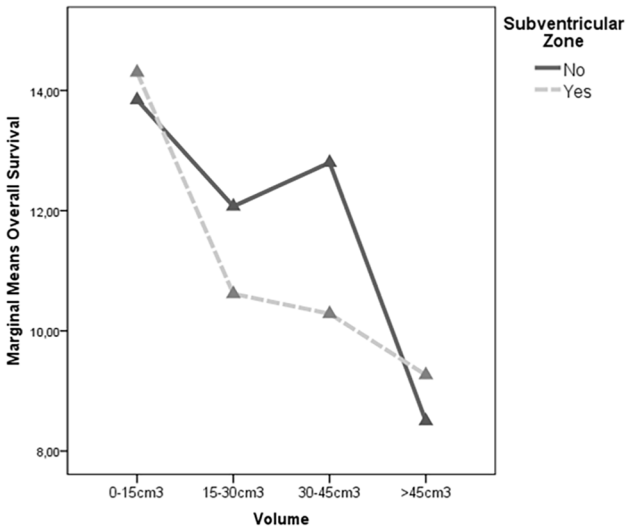

Fig. 5a. Multivariate ANOVA analysis disclosing the effect of Volume and Subventricular Zone on Overall Survival.

coherently with was expected for a homogeneous cohort of GBM (OS-PFS r.806; EOR-OS r.235; EOR-PFS r.630; p. between 0.001 and 0.004).

4. Discussion

SVZ embodies the most important niche of NSCs which present self-renewal and proliferative capacities, making them the possible progenitor cells from which GB originates (Fig. 8) [10,27,28,29]. NSCs in the SVZ are located in the subependymal zone, surrounded by ependymal cells, vascular endothelial cells, astrocytes, and oligodendrocytes, which play a critical role in supporting the stem cells and controlling the proliferation rate.

Even in GBs arisen far from the SVZ and undergone to a surgical GTR, the remaining GB stem cells (GSCs) left behind would be able to migrate from the tumor mass and to colonize the SVZ, leading to a disease recurrence, characterized by a reduced response to chemo/radiotherapeutic treatments [30,31].

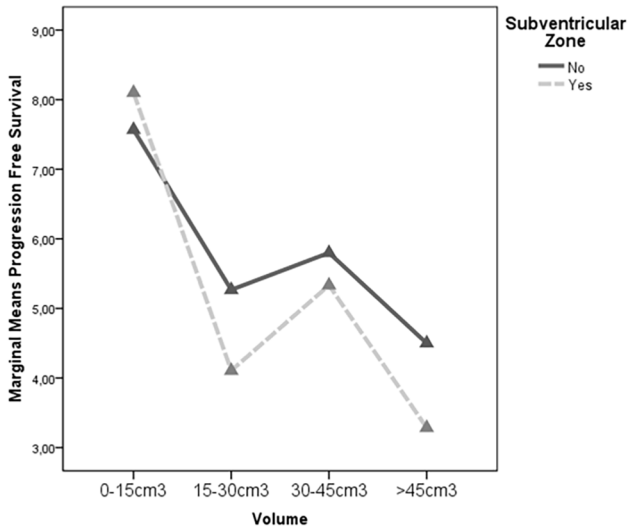

Fig. 5b. Multivariate ANOVA analysis disclosing the effect of Volume and Subventricular Zone on Progression Free Survival.

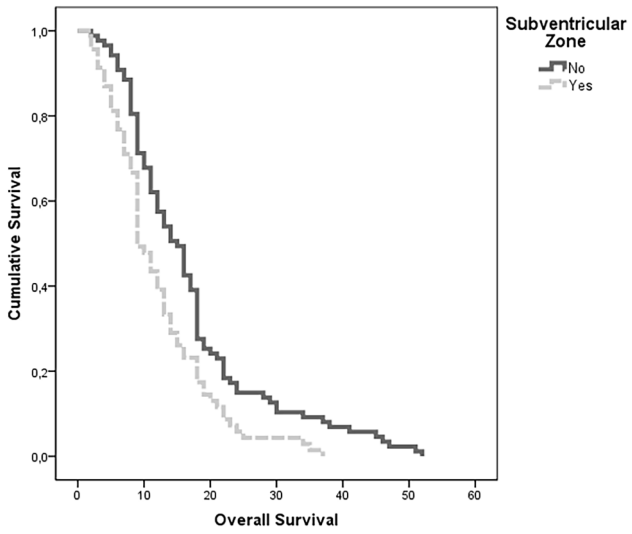

Fig. 6. Multivariate ANOVA analysis disclosing the effect of Age and Subventricular Zone on Overall Survival.

Although numerous investigations have tried to classify different subtypes of GB using molecular markers correlating with OS and PFS parameters [1,2,3,5], the impossibility to precisely stratify the different survival outcomes on the exclusive ground of the molecular pattern of the lesions [36], defines the most significant problem in our fine understanding of the oncology of GB [44].

Moreover, some authors assessed a possible predictive role of the topographic location of the lesion in regards to their biological signatures and clinical outcomes [12,18].

Patients with GBM contacting the SVZ have basically lower survival [49]. This effect may be independent of the common predictors of GBM survival, suggesting a clinical influence of V-SVZ contact on GBM biology.

Ventricular or periventricular GBs involving SVZ, could represent a special subcohort of High Grade Gliomas with unique features.

In our study results, V-SVZ GB is greater tumors at presentation, clinically associated with Headache and Sensory Disturbances, which are associated with a higher risk of partial resection and with a less satisfactory functional outcome in the early postoperative period. Although from the histochemical point of view the two subgroups did

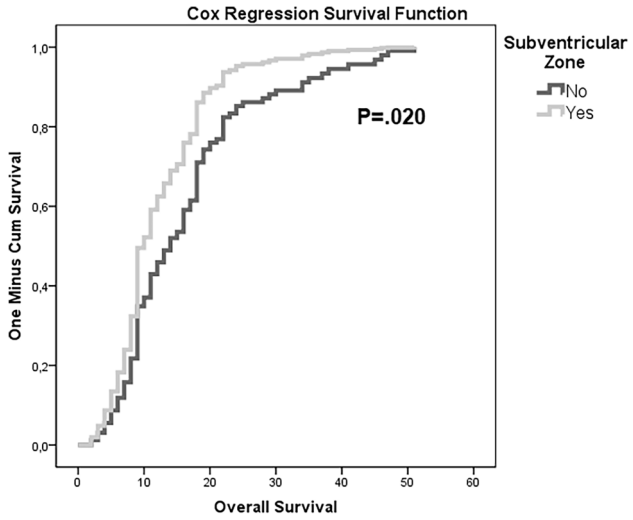

Fig. 7a. Regression Model Survival Curve disclosing the Survival Charts in respect to Overall. The recurrence rate from PFS between the two groups shows differences that agree much more with GTR and size rather than with localization, therefore it seems that the prognostic impact is on overall survival as a negative prognostic finding in SVZ +.

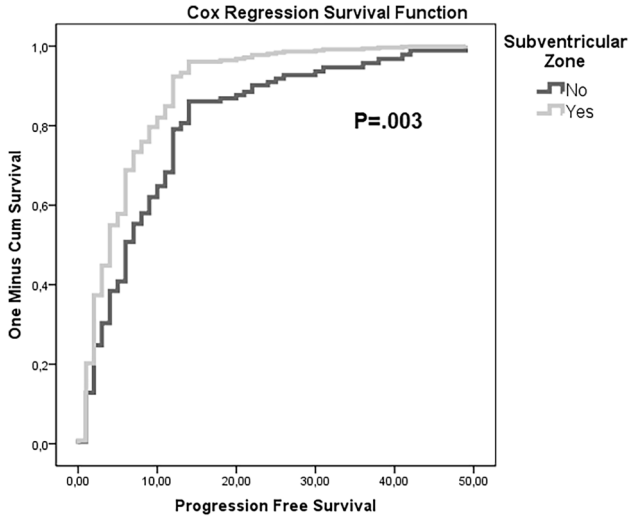

Fig. 7b. Regression Model Survival Curve disclosing the Survival Charts in respect to Progression Free Survival. The recurrence rate from PFS between the two groups shows differences that agree much more with GTR and size rather than with localization, therefore it seems that the prognostic impact is on overall survival as a negative prognostic finding in SVZ +.

not show relevant differences in concerns to the expression of the IDH mutation, EGFR, and Ki67 overexpression [47], p53 mutation (except for MGMT methylation status with a higher incidence in V-SVZ GB and exception done for the IDH expression, for which the numbers do not allow a real statistical comparison), our multivariate analysis demonstrated a clear and statistically significant survival advantage of cortical GBM over V-SVZ GB.

Other previous multivariate analyzes have been presented in the literature adjusted for age, sex, KPS, EOR, postoperative treatment and tumor volume, but V-SVZ contact has not been identified as an independent predictor of survival [14]; SVZ + tumors are major presenting tumors that are associated with an increased risk of partial resection and with a less satisfactory functional outcome in the early postoperative period. However, correlations with volume and GTR alone do not justify the clinical and prognostic trend of SVZ + tumors, as evidenced in other smaller series [46] but focused on post-operative complications.

Moreover, we propose that the aforementioned detrimental effect on survival outcomes could be independent of the remaining independent predictors of survival in GB patients such as namely: Age, KPS, EOR and adjuvant treatments pointing out to a completely distinct bio pathology of GBMs with and without SVZ contact. Only a few studies focused on the molecular pattern of SVZ + GBMs and SVZ − GBs, even demonstrating no clear association of such subgroups of GB with a distinct molecular pattern [19,20,22,48].

The V-SVZ is known to harbor pluripotent neural stem cells, thus increasing the propensity to generate aggressively proliferating tumors [2–4]. Some retrospective analysis [17] outlines that the pro-neural and neural GB subtypes are located close to SVZ either.

A study of Jafri et al. [15] demonstrated that V-SVZ tumors are more likely to recur distantly from the initial lesion, which may, in part, explain the poorer prognosis of such subgroup of patients, in our study the SVZ + GBs had a worse post-procedural KPS than SVZ-GBs, with could be possible for the depth of location of the lesion and for major difficult to remove the mass without determining neurological deficits, though there isn't a statistical difference about this factor.

In our cohort, it was not possible to disclose a significant difference in regards to demonstrated prognostic specific factors IDH1-2, EGFR and p53 mutation between SVZ + GBs and SVZ - GBs despite some studies identify variabilities to these specimens [21,45], according to with our data recent studies evidence [8,31,32] that cancer derives from an accumulation of somatic mutations resulting in an altered proteome associated to an uncontrolled proliferation as well as selective growth advantage, protein expression analysis of both SVZ + and SVZ − GBs may reveal protein signatures specific for SVZ + GBs, recently introduced in molecular diagnostics analysis [5] such proteins-hemopexin (HPX), apolipoprotein A1 (APOA1) and alpha-1-antichymotrypsin (SERPINA3).

To date, despite all the advances in proteomics, and the results of the available literature suggesting a possible role of SVZ in the survival of GB patients [6,7], a huge void in the full understanding of a possible role of these proteins in the survival of the patients is still present.

The aforementioned findings [2,3,6,7,14,17], brought several investigators to the promising hypothesis that irradiating the SVZ may extend survival in GB [16]. Current evidence is unfortunately still limited by incomplete study designs and inconsistent survival outcomes, the absence of an undisputed "effective dose" and even an undisputed definition of "SVZ area".

The identification of GSCs and their origin raises hope to identify new molecular, epigenetic and genetic targets for the development of combination therapies to erase tumor cells as well as BTPCs [8,9,23].

The present study is the largest consecutive series concerning this specific topic. The current classification of GBM identifies different prognostic subtypes of patients based on the molecular status, but we strongly suppose that location and the relationship with SVZ matters.

It would be interesting if, in the future, we could perform different histological analysis between the part of the tumor-infiltrating SVZ and the rest of it, in a larger cohort of patients to increase the confidence of the conclusion that GB contact with the LV is an independent predictor of survival.

5. Limitations of the present study

This collection of data was performed from the same group analyzing the same data set of a previous report of GB, the manuscripts should be considered independently because they may differ in their analytic methods, interpretation and conclusions. Another limitation is the lack of information concerning the possible salvage therapies performed on patients in the last weeks/months of their life, although unclear oncologic information was an exclusion criterion, additional information for a limited number of patients could have been not completely provided during the data collection. Further limitations of the present

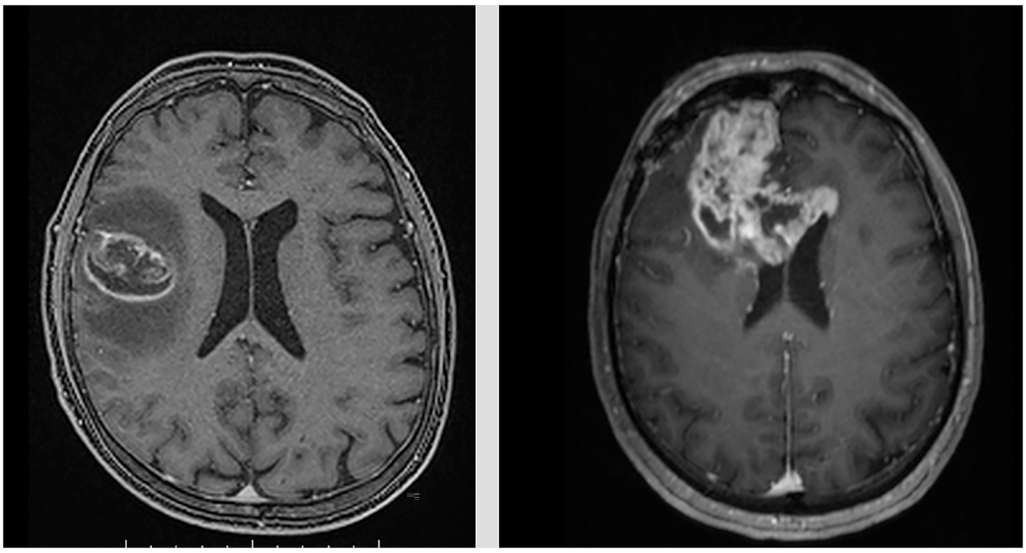

Fig. 8. A MRI images showed 2 sample cases of periventricular and subcortical GBMs in T1 weighted axial sequences.

investigations are its retrospective nature, and the possible biases derived from the relative exiguity of the cohort, which nevertheless presents a fair statistical power of the study. Furthermore, size was demonstrated to be an independent predictor of OS, and since large size implies a higher chance of the tumor to reach the ventricle surface, this represents a major bias. In fact, tumor in the SVZ + group was larger than SVZ- group. Other investigations are already ongoing, in our Institution, to improve treatments, prolong survival, and lower risks for patients suffering from high-grade gliomas.

6. Conclusions

Identification of prognostic indicators of survival in patients with GB is important to achieve effective, patient-specific and tailored treatments to increase survival and improve the quality of life. The contemporary, still limited range of therapeutic options, combined with a poor response to currently used therapies, increased the pressure to discover new genetic, epigenetic and molecular pathways involved in the pathogenesis of GBs. In the present study, we described the anatomical contact of the lesion with the V-SVZ as a significant independent predictor of poor oncologic outcome in GB patients.

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. The authors confirm their adherence to ethical standards and have NO financial disclosures that would be a potential conflict of interest with this publication.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comitato Etico Università "Sapienza" di Roma Policlinico Umberto I, istituito ai sensi del DM 08.02.2013, con deliberazione regionale n. 146 del 12–06-2013 e con delibera di istituzione dell'Azienda Policlinico Umberto I n. 000,442 del 15.07.2013 così come integrata con delibera N° 000,731 del 20.11.2013) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors.

Informed consent

Informed consent was obtained from all individual participants included in the study.

The patient has consented to the submission of this review article to the journal.

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CRediT authorship contribution statement

Daniele Armocida: Conceptualization. **Alessandro Pesce:** . **Mauro Palmieri:** Writing - review & editing. **Giancarlo D'Andrea:** Supervision. **Maurizio Salvati:** Supervision. **Antonio Santoro:** Supervision. **Alessandro Frati:** Conceptualization, Supervision.

Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome. We wish to draw the attention of the Editor to the following facts which may be considered as potential conflicts of interest and to significant financial contributions to this work.

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