ORIGINAL ARTICLE

Seizure-susceptible brain regions in glioblastoma: identification of patients at risk

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Background and purpose: The main aim of this study was to identify which patients with glioblastoma multiforme (GBM) have a higher risk of presenting seizures during follow-up.

Methods: Patients with newly diagnosed GBM were reviewed (n = 306) and classified as patients with (Group 1) and without (Group 2) seizures at onset. Group 2 was split into patients with seizures during follow-up (Group 2A) and patients who never had seizures (Group 2B). The anatomical location of GBM was identified and compared by voxel-based lesion symptom mapping (discovery set). Seizure-susceptible brain regions obtained were assessed visually and automatically in external GBM validation series (n = 85).

Results: In patients with GBM who had no seizures at onset, an increased risk of presenting seizures during follow-up was identified in the superior frontal and inferior occipital lobe, as well as in inferoposterior regions of the temporal lobe. Conversely, those patients with GBM located in medial and inferoanterior temporal areas had a significantly lower risk of suffering from seizures during follow-up. Additionally, the seizure-susceptible brain region maps obtained classified patients in the validation set with high positive and negative predictive values.

Conclusions: Tumor location is a useful marker to identify patients with GBM who are at risk of suffering from seizures during follow-up. These results may help to support the use of antiepileptic prophylaxis in a selected GBM population and to improve stratification in antiepileptic clinical trials.

Introduction

Seizures are common in glioblastoma multiforme (GBM) [1,2]. Approximately 20%–30% of patients experience seizures as the initial symptom and 10%–30% will present seizures during follow-up [1–5]. Brain tumor-related epilepsy (BTRE) has been associated with a decreased quality of life and it is considered a risk factor for long-term disability [6]. This fact might explain the extended use of antiepileptic drug (AED) prophylaxis (up to 50%) [3,4] in large GBM population studies world-wide, in contrast to the recommendations of the American Academy of Neurology [7]. A correct identification of patients at risk of developing epilepsy after GBM diagnosis would not only have an impact on the clinical setting by allowing a more accurate judgment of AED prophylaxis treatment but would also facilitate a better stratification of patients with GBM in clinical trials focused on AED.

In the present study, we analysed whether the anatomical location of the GBM, using magnetic resonance imaging (MRI) voxel-based lesion symptom mapping (VLSM) [8], could identify those areas with

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a high risk of developing seizures during follow-up. The data generated were subsequently validated in two additional series.

Methods

Patients

Medical records from newly diagnosed patients with histologically confirmed GBM (2007–2013) were reviewed from the Hospital Universitari de Bellvitge–ICO l'Hospitalet database. Patients with prior history of glioma were excluded. Patients were included if they had an available baseline brain MRI with gadolinium-enhanced T1-weighted (Gd-enhanced T1) images and classified as GBM with (Group 1) and without (Group 2) seizures at onset. Group 2 was split into patients with seizures during follow-up (Group 2A) and patients who never had seizures (Group 2B) (Fig. 1). All patients included had died by the end of the follow-up period (December 2015). Patients were excluded if they had a previous diagnosis of non-related tumor epilepsy, had a multicentric or infratentorial tumor, were on prophylactic AED, the diagnosis of epilepsy was doubtful or the information in medical records was not complete. Clinical baseline data and brain tumor-related characteristics were also collected. To conduct an external validation, 41 patients with primary GBM at the Hospital Clínic de Barcelona and 44 at the Clínica Universidad de Navarra, diagnosed during the same period and with the same inclusion and exclusion criteria, were reviewed. The protocol was approved by the Ethical Committee of Hospital Universitari de Bellvitge–ICO l'Hospitalet (PR 128/16). Informed consent was not required due to the retrospective nature of the study and to the fact that, by the end of the follow-up period, all of the patients had died.

Magnetic resonance imaging data

Scans were performed using 1.5-T MRI (Intera, Philips Medical System, Best, The Netherlands). A Gd-enhanced T1 sequence (slice thickness, 5 mm with 0.5-mm gap; echo time, 15 ms; repetition time, 540 ms; field of view, 230 mm; 256 × 256 resolution; voxel size, 0.9 × 0.9 × 5.0 mm) was used. Registering magnetic resonance images to a common space was necessary to compare different groups of individuals. In order to achieve optimal registration with no post-transformation out-of-brain distortion or lesion shrinkage [9], cost function masking was applied [10]. Masks, depicting the tumor, were drawn in native space over the Gd-enhanced T1 for each patient by two experienced neurologists, using MRIcron (http://www.mccauslandcenter.sc.edu/mricro/mricron). Contrast-enhanced areas were identified as tumor areas. If there was >5% discrepancy between neurologists using the Bland–Altman plot, the mask used was the one drawn by the senior neurologist. Using SPM8

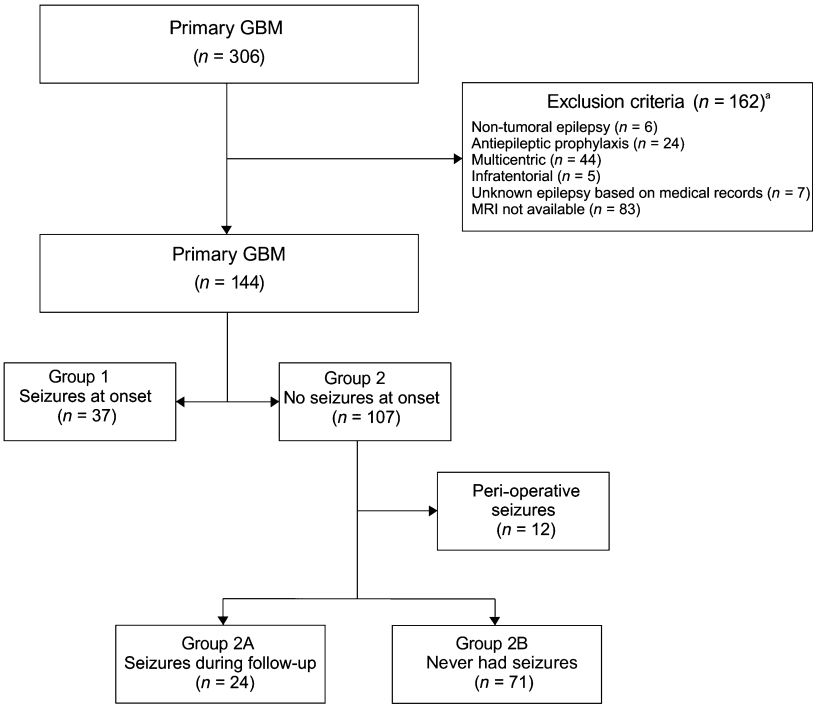

Figure 1 Flow diagram. [a]Seven patients were included in two different exclusion criteria. GBM, glioblastoma multiforme; MRI, magnetic resonance imaging.

(http://www.fil.ion.ucl.ac.uk/spm/software/spm8), Unified Segmentation [11] was then applied in order to register the Gd-enhanced T1 image and the tumor mask for each patient to the Montreal Neurological Institute space. All masks were flipped to the left hemisphere to focus the analysis on the anatomical localization without regarding to lateralization.

In addition, the differences in the degree of tumoral gray matter (GM)/white matter (WM) involvement in each group were also explored (Appendix S1).

Voxel-lesion symptom mapping

The normalized binary lesion maps were used to calculate a VLSM analysis based on the primary location of tumors. Each voxel was analysed and the presence or absence of a lesion (tumor) was correlated with behavioral data (pre-determined BTRE groups) [8] using the Non-Parametric Mapping toolbox (version 6 June 2013) included with MRIcron (Brunner–Munzel test) [12]. Permutation testing (family-wise error, $n = 1\ 000$, $P = 0.025$) was used to correct for multiple comparisons. Based on the aforementioned BTRE classification of our cohort, five comparisons were calculated to respond to three questions. (i) Which brain regions are related to BTRE at onset? We compared patients with GBM with seizures at onset (Group 1) versus those with no seizures at onset (Group 2). (ii) Which regions are related to BTRE during follow-up? We compared patients with GBM with seizures during follow-up (Group 2A) versus Group 1 and Group 2B (never had seizures). (iii) Which regions are related to non-BTRE? Group 2B was compared with Group 1 and Group 2A.

The 'seizure-susceptible brain area' was defined as the largest cluster of significant voxels acquired by this method. The statistical maps obtained were related to anatomical structures using the Automated Anatomical Labeling atlas for GM and the Johns Hopkins University atlas for WM [13].

Validation of voxel-based lesion symptom mapping: identified regions

Two seizure-susceptible brain maps (seizures during follow-up and never had seizures) were created from the z-maps obtained during the VLSM analysis. The seizures during follow-up map was obtained by including the comparison between Group 2A (seizures during follow-up) and Groups 1 and 2B. The never had seizures map was obtained from comparison between Group 2B (never had seizures) and Groups 1 and 2A. Both maps were validated by using a visual inspection and an automatic method by examining a group of 85 patients with GBM. Visual inspection validation consisted of a qualitative visual classification of the baseline (pre-surgery) Gd-enhanced T1 MRI. Each individual tumor of the validation set was classified as being involved/not involved. We considered involvement if the tumor was totally or partially placed within the masks. Multivariate pattern analysis (MVPA) was carried out for the automatic method [14]. For both methods, a binary classification accuracy assessment was performed using receiver operating characteristic curves.

Results

Demographic and clinical data

Patients' characteristics are summarized in Table 1. Seizures at onset (Group 1) were reported in 37 (26%) patients, 24 (17%) had seizures during follow-up (Group 2A) and 71 (49%) never had seizures (Group 2B). Twelve (8%) patients with peri-operative seizures (seizures during neurosurgery or up to 7 days post-surgery) were excluded. Median time from GBM diagnosis to the first seizure in Group 2A was 6.2 (0.4–23.9) months.

Patients in Group 1 were younger ($P = 0.008$), had more preferentially lobar location ($P = 0.008$) and smaller size ($P = 0.001$) than patients in Group 2B. Additionally, patients in Group 2B had worse median Karnofsy Performance Scale score ($P = 0.002$), underwent more incomplete resections ($P = 0.005$) and biopsies ($P = 0.005$), and were under palliative care ($P = 0.01$) more frequently than the other groups. Consequently, Group 2B had worse overall survival (OS) ($P < 0.001$) in the univariate analysis.

Concerning survival, Cox regression multivariate analysis, including age, extent of surgery, Karnofsy Performance Scale score, post-surgical treatment and epilepsy at onset, identified age [hazard ratio (HR), 1.025; 95% confidence interval (CI), 1.003–1.048; $P = 0.026$], extent of surgery (HR, 2.548; 95% CI, 1.47–4.416; $P = 0.003$), Karnofsy Performance Scale score (HR, 0.344; 95% CI, 0.205–0.579); $P < 0.001$) and post-surgical antitumor treatment (HR, 0.280; 95% CI, 0.147–0.531; $P < 0.001$) as the only prognostic independent variables. Epilepsy at onset was not significantly associated with prolonged OS (HR, 1.125; 95% CI, 0.710–1.783; $P = 0.616$).

The right/left distribution of GBM was very similar in all groups [Group 1, 22 (59.5%)/15(40.5%) ($X^2 = 1.32$, $P = 0.32$); Group 2A, 12(50%)/12(50%) ($X^2 = 0$, $P = 1$); Group 2B, 37(52.1%)/34(47.9%) ($X^2 = 0.127$, $P = 0.81$)]. Also, there were no differences regarding the degree of tumoral GM and WM involvement (Wilcoxon's test: Group 1, $P = 0.78$;

Table 1 Characteristics of the cohort

	Group 1 (n = 37)	Group 2A (n = 24)	Group 2B (n = 71)	P-value
Age (years)	56.73 ± 11.19	57.75 ± 11.91	63.75 ± 11.01	<0.01[a]
Gender				ns
Male	27 (73)	16 (66.7)	39 (54.9)	
Female	10 (27)	8 (33.3)	32 (45.1)	
Lesion location				<0.05[ab]
Lobar	32 (86.5)	15 (62.5)	44 (62)	
Other locations				
CC	1 (2.7)	0 (0)	4 (5.6)	
Lobar + CC	2 (5.4)	8 (33.3)	16 (22.5)	
Lobar + BG	2 (5.4)	1 (4.2)	4 (5.6)	
Others	0 (0)	0 (0)	2 (2.8)	
Tumor size (cm^3)	27.5 ± 24.7	48,1 ± 32.5	52,2 ± 35.4	<0.01[ab]
% tumoral GM voxels	42 ± 17.2	35 ± 16.1	41 ± 15.6	ns
% tumoral WM voxels	40 ± 18.6	48 ± 19.4	41 ± 14.6	ns
KPS	80 (50–100)	80 (50–100)	70 (10–100)	<0.05[ac]
Surgery				<0.01[ac]
Biopsy	8 (21.6)	2 (16.7)	30 (42.3)	
Partial resection	13 (35.1)	15 (62.5)	28 (39.4)	
Complete resection	16 (43.2)	7 (29.2)	13 (18.3)	
Treatment				<0.05[ac]
CT + RT	29 (78.4)	19 (79.2)	33 (46.5)	
RT	5 (13.5)	2 (8.3)	13 (18.3)	
Palliative care	3 (8.1)	2 (8.3)	22 (31)	
Unknown	0 (0)	1 (4.2)	3 (4.2)	
Progression				ns
Yes	34 (91.9)	23 (95.8)	62 (87.3)	
No	2 (5.4)	1 (4.2)	5 (7)	
Unknown	1 (2.7)	0 (0)	4 (5.6)	
OS (months)	16.6 (0.1–58.5)	18.4 (0.6–55.4)	5.3 (0.2–47.2)	<0.01[ac]

BG, basal ganglia; CC, corpus callosum; CT, chemotherapy; GM, gray matter; KPS, Karnofsy Performance Scale; ns, no significant differences (P > 0.05); OS, overall survival; RT, radiotherapy; WM, white matter; One-way ANOVA test was used to compare group means and Bonferroni test was applied as post-hoc test. Non-parametric, Kruskal–Wallis and chi-square tests were used to compare group medians and percentages. Log-rank test was used to compare survivals. Data are given as mean ± SD, n (%) and median (range); [a]Statistical differences between Group 1 and Group 2B; [b]Statistical differences between Group 1 and Group 2A; [c]Statistical differences between Group 2A and Group 2B.

Group 2A, P = 0.152; Group 2B, P = 0.77). There was neither greater tumor GM (P = 0.27) nor WM (P = 0.24) involvement in one group compared with the others.

Seizure-susceptible brain areas (voxel-based lesion symptom mapping analysis)

Of the 306 patients initially reviewed, 144 fulfilled the inclusion criteria (Fig. 1). Discrepancy between the neurologists was 0.7% (165 mm^3; 62 voxels).

The brain tumor areas related to seizures at onset (Group 1) were superior and posterior frontal areas (supero-posterior part of the middle frontal gyrus, precentral gyrus and rolandic operculum), as well as anterior parietal areas (postcentral gyrus), the insula and Heschl gyrus located in the superior temporal lobe (Fig. 2a). In the group of interest (Group 2), the brain areas significantly associated with a higher risk of suffering from seizures during follow-up (Group 2A) were in medial regions of the superior frontal gyrus, supplementary motor area, supero-anterior middle frontal gyrus, medial–anterior cingulate gyrus, anterior–superior corona radiate and medial-inferior occipital regions (calcarine cortex and cuneus) as well as the genu-body of the corpus callosum, caudate and in the posterior region of the inferior temporal and fusiform gyrus (Fig. 2b). Conversely, those patients with GBM located in medial temporal areas (posterior region of hippocampus and parahippocampus, amygdala, subcortical part of middle temporal gyrus and also medial WM tracts including the sagittal stratum, retrolenticular part of internal capsule, posterior thalamic radiation and fornix) as well as the anterior region of the inferior temporal and fusiform gyrus had a significantly lower risk of suffering from seizures during follow-up (Group 2B) (Fig. 2c and Table S1).

Validation set

Only patients with no seizures at onset were included in the validation set. Overall, 29% (12/41) of patients

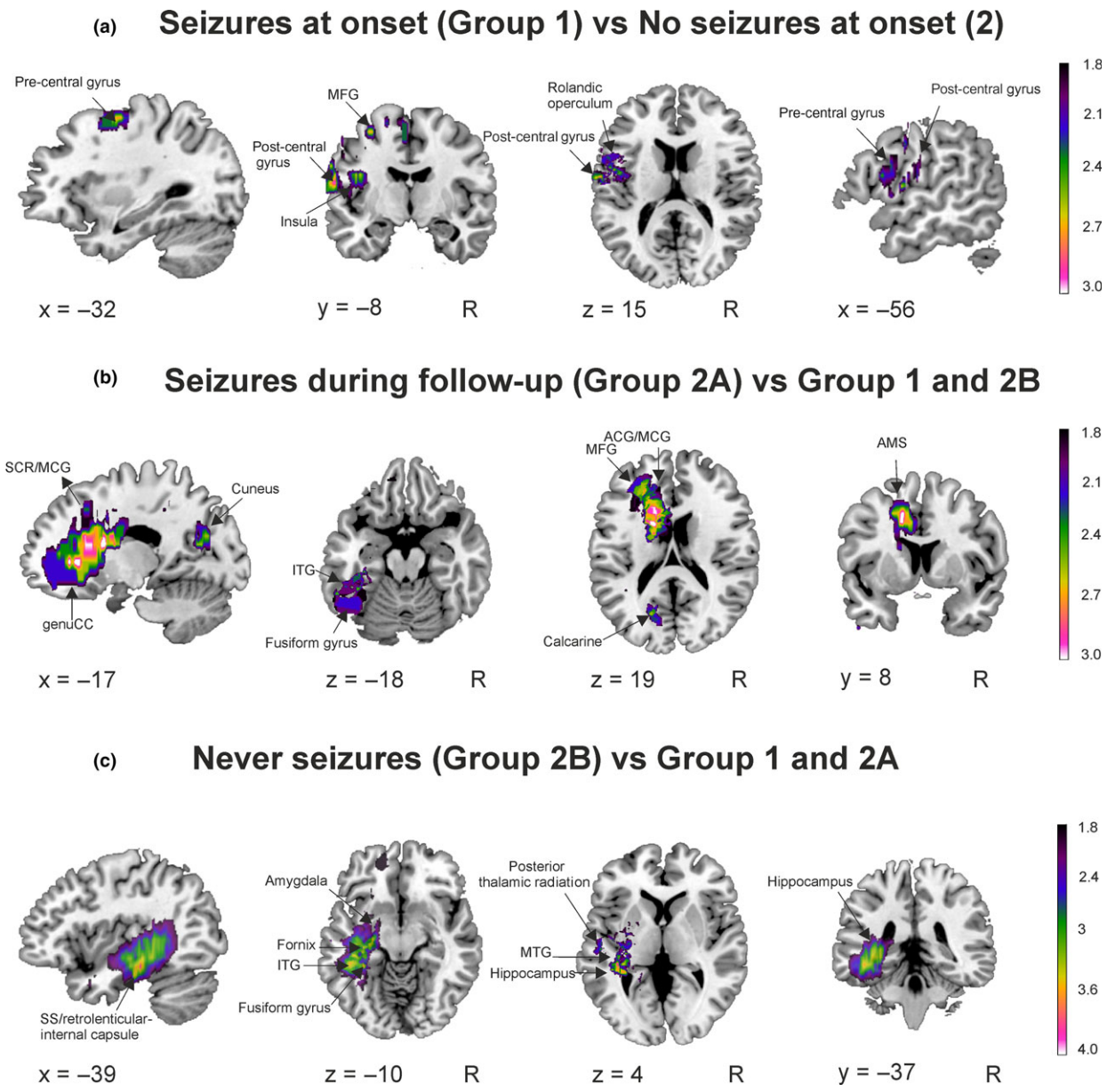

Figure 2 Voxel-based lesion symptom mapping analysis between brain tumor-related epilepsy groups. (a) Seizures at onset (Group 1) versus no seizures at onset (Group 2); (b) seizures during follow-up (Group 2A) versus Groups 1 and 2B; (c) never had seizures (Group 2B) versus Groups 1 and 2A. Significant differences between groups (z-score maps) are shown at family-wise error-corrected $P < 0.025$ and superimposed on a standardized T1 template in Montreal Neurological Institute coordinates. The threshold bar (right side) represents z-score values: cold to warm colors represent lower to higher significance, respectively. ACG, anterior cingulate gyrus; AMS, supplementary motor area; CC, corpus callosum; ITG, inferior temporal gyrus; MCG, medial cingulate gyrus; MFG, middle frontal gyrus; MTG, middle temporal gyrus; R, right; SCR, superior corona radiata; SS, sagittal stratum.

from the Hospital Clínic de Barcelona and 30% (13/44) from the Clínica Universidad de Navarra had seizures during follow-up. Patients ($n = 85$) were visually classified as developing seizures during follow-up with a sensitivity of 50%, specificity of 79%, positive predictive value (PPV) of 48% and negative predictive value (NPV) of 80%, and as not developing seizures with a sensitivity of 77%, specificity of 55%, PPV of 81% and NPV of 48%. The MVPA classification performance was highly accurate (Fig. 3). Patients were classified as developing seizures with a sensitivity of 92%, specificity of 81%, PPV of 67% and NPV of

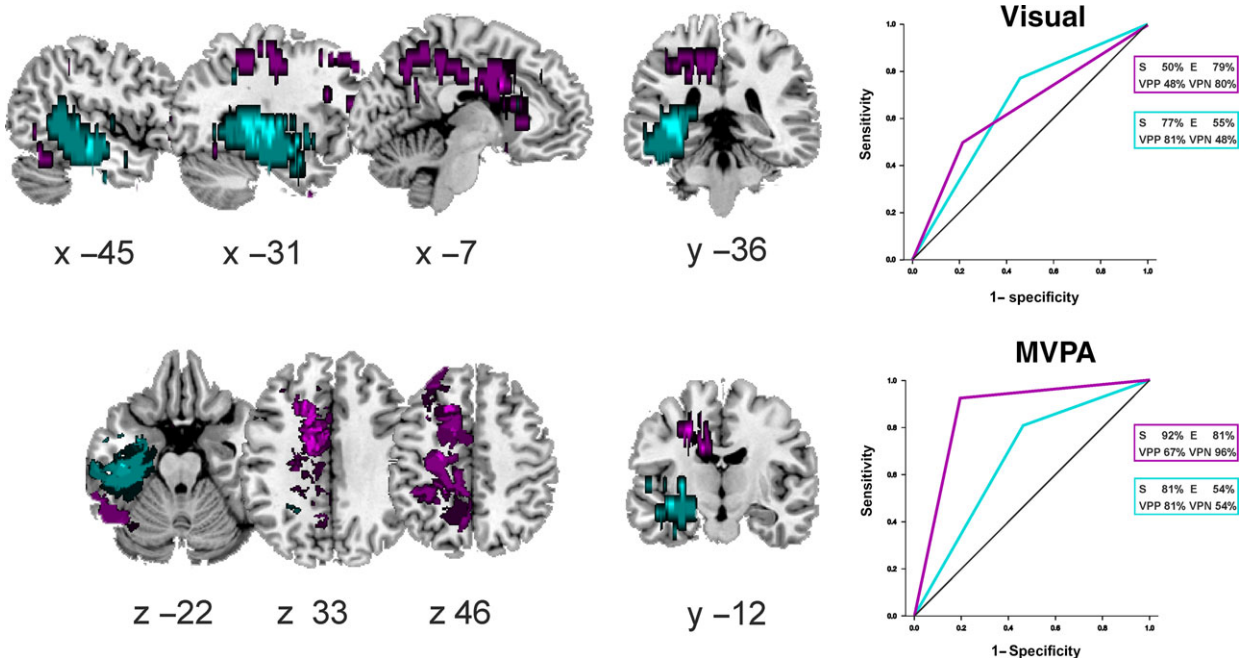

Figure 3 Glioblastoma multiforme seizure-susceptible brain maps and validation results. Seizure-susceptible brain maps created from the z-maps obtained during the voxel-based lesion symptom mapping analysis. Purple, seizures during follow-up map; pale blue, never had seizures map. Receiver operating characteristic curves for visual and multivariate pattern analysis (MVPA) are shown. E, specificity; S, sensitivity; VPP, positive predictive value; VPN, negative predictive value.

96%, and as not developing seizures with a sensitivity of 81%, specificity of 54%, PPV of 81% and NPV of 54%. Both seizure-susceptible brain maps (seizures during follow-up and never had seizures) are available for open use at http://brainvitge.org/z_oldsite/msimo/Seizure_maps.rar.

Discussion

Our study demonstrates for the first time, using a VLSM analysis, a significant association between GBM location and the risk of presenting seizures during follow-up. Among patients with no seizures at onset, those with GBM located in medial superior frontal and inferior occipital lobe, together with inferoposterior regions of temporal lobe, had a higher risk of suffering seizures during follow-up. Conversely, patients with GBM located in medial and inferoanterior regions of temporal lobe had a lower risk of suffering seizures during follow-up. These results were externally validated visually and automatically, exhibiting, mostly with the automatic method, high PPV and NPV.

Previous studies proposed that glial tumors located in frontal, parietal, insular and temporal lobes were more epileptogenic [2,15]. However, most of these studies did not use a volumetric imaging analysis for precise localization of seizure-related regions. In contrast to our results, one retrospective volumetric study [16] (n = 67) in a mixed sample of high-grade gliomas reported that tumors located in corpus callosum, medial–anterior cingulate gyrus and caudate have a lower risk of seizures at onset while no brain region showed an increased seizure risk. These different results could be explained by the histological heterogeneity of the sample and the lack of consideration as a separate group of the analysis of patients who develop seizures during follow-up. Another disparity from our study is that they used a clustering algorithm volumetric analysis. To date, to the best of our knowledge, only a study using VLSM in low-grade glioma has been published [17], showing that inferior and middle frontal gyrus were associated with seizures at onset.

Overall, the addition of a more precise brain mapping using VLSM has defined distinct seizure-risk brain regions within the same lobe. Although posterior areas of the frontal lobe were associated with seizures at onset, the medial and superior areas were associated with seizures during follow-up. With regard to seizure susceptibility in temporal lobe, the most superior and peri-rolandic operculum of superior temporal lobe was associated with seizures at onset, the inferoposterior regions were related to seizures during

follow-up, and the medial and inferoanterior regions were related to a lower risk of suffering from seizures. This interesting finding is, in fact, contrary to previous literature on the epileptogenicity of medial temporal lobe in non-BRTE populations [18]. However, studies focused on temporal lobe epilepsy noted the relevance of extramesial areas [19,20], describing an epileptogenic network with a primary temporal lobe zone extending to neighboring regions. Thus, these studies highlight the relevance of this complex epileptogenic network triggering seizures rather than a confined structure, and also the role of the integrity of WM pathways in propagating the epileptic activity [21]. In our cohort, there were no significant differences regarding tumoral GM or WM involvement between the groups. In brief, all of these findings support the fact that tumor location plays an important role in developing seizures in GBM [2,15].

In addition, our validation results highlighted the consistency of the seizure-susceptible brain region maps. Regarding the seizure during follow-up map, both validation methods exhibited high specificity values, but only the MVPA analysis was associated with a high sensitivity. One possible explanation is that voxels within the same brain region do not contribute in the same degree to the epileptogenesis, a feature that only MVPA takes into consideration.

This study, however, had some limitations. It was retrospective in nature, the fluid-attenuated inversion recovery images were not included because they do not differentiate edema from tumor, thus potentially overestimating tumor brain areas, and we also used a strict exclusion criterion to obtain a homogeneous cohort, which may have decreased our sample size (although the inferred post-hoc statistical power was between 0.6 and 0.8). In addition, patients in Group 2B (never had seizures) had a shorter OS rate compared with the other groups, being at less risk of having seizures because they survive for a shorter time. However, we observed that nearly 40% of patients in Group 2B died without presenting seizures after the median time from GBM diagnosis to the first seizure in Group 2A (6.2 months). Thus, the shorter OS of Group 2B would not explain why none of these patients presented seizures during follow-up. Finally, the lack of molecular information in our cohort of patients with GBM (e.g. isocitrate dehydrogenase 1 mutation status [22]) might explain our failure to achieve predictive values around 100%.

In conclusion, our study demonstrates that GBM location is significantly associated with the risk of suffering from seizures during follow-up. Our results provide a precise seizure-susceptible brain tumor map that allows classification of those patients with GBM with no seizures at onset with a high or low risk of suffering from seizures in the future. A correct identification of patients at risk of developing epilepsy would not only have an impact on the clinical setting but would also facilitate a better stratification of patients with GBM in clinical trials focused on AED.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Glioblastoma multiforme location associated with epilepsy. Results are shown at $P < 0.025$. Montreal Neurological Institute coordinates are used
Appendix S1. Supplementary methods.

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