Multimodal imaging of brain tumors
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CHAPTER 4

Subventricular zone involvement characterized by diffusion tensor imaging in glioblastoma

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P.J. van Laar, A. van der Hoorn, S.J. Price.

ABSTRACT

Background: Glioblastomas have a poor prognosis, possibly because of a subpopulation of therapy-resistant stem cells within the heterogeneous glioblastoma. Because the subventricular zone is the main source of neural stem cells, we aimed at characterizing the subventricular zone using diffusion tensor imaging (DTI) to show subventricular zone involvement in glioblastoma.

Methods: We prospectively included 93 patients with primary glioblastomas who underwent preoperative DTI. The nonenhancing high fluid-attenuated inversion recovery (FLAIR) signal was used to describe the infiltrative tumor margin. We used a 5-mm margin surrounding the lateral ventricles to define the subventricular zone. The subventricular zone with high FLAIR was compared with the subventricular zone without high FLAIR, control high FLAIR outside the subventricular zone and control contralateral normal-appearing white matter. Normalized DTI parameters were calculated and compared between the different regions.

Results: The subventricular zone with high FLAIR showed increased isotropic p values compared with the subventricular zone without high FLAIR (t126 = 3.9; P < 0.001) and control regions (t179 = 1.9; P = 0.046). Anisotropic q and fractional anisotropy values were lower in regions with high FLAIR compared with the subventricular zone without high FLAIR (t181 = 11.6, P < 0.001 and t184 =12.4, P < 0.001, respectively).

Conclusion: DTI data showed that the subventricular zone is involved in glioblastoma with increased isotropic p values in the subventricular zone with high FLAIR, indicating tumor infiltration.
INTRODUCTION

Glioblastoma (GBM) is the most prevalent primary malignant brain tumor in adults.\(^1\) It is associated with most years of life lost despite aggressive therapy consisting of maximal safe resection followed by radiotherapy and concomitant and/or adjuvant temozolomide chemotherapy.\(^2,3\) GBMs are heterogeneous tumors for which local recurrence is unavoidable because of the locally invasive behavior of these tumors.\(^4\) This local recurrence might result from a subpopulation of neural stem cells within the heterogeneity of GBM that are relatively resistant to the current therapy.\(^5\)

The subventricular zone (SVZ) harbors the largest population of neural stem cells in the brain.\(^6\) These stem cells were found to be astrocyte precursors that could generate multipotent neurospheres in vitro under the influence of epidermal growth factor and fibroblast growth factor.\(^6-9\) In animals, these stem cells were capable of migrating away from the SVZ.\(^6,7\) Furthermore, fully differentiated astrocytes are less susceptible to malignant transformation than are neural stem cells.\(^10\) Hence, neural stem cells from the SVZ have received increasing interest as the possible cell of origin in GBM.

Despite the importance of the SVZ in relation to tumor initiation and the local recurrence of GBM, only a few imaging studies have focused on the SVZ, mainly relying on conventional magnetic resonance imaging (MRI). However, it is known that conventional MRI does not show the local invasion of GBM that is present outside the contrast enhancement.\(^11\) More advanced MRI methods, such as diffusion, better represent the biological behavior and could identify areas of tumor invasion.\(^12,13\)

We have previously histologically verified that diffusion tensor imaging (DTI) can show tumor infiltration and disruption of peritumoral white matter outside the contrast enhancement in GBM.\(^11\) Because GBM has the tendency to infiltrate along white matter tracts, DTI can detect subtle white matter changes by decomposing the diffusivity into a pure isotropic component (p) and a directional anisotropic component (q).\(^14\) In our image-guided biopsy study we showed that infiltration by tumor cells can be identified by elevated isotropic p components because of vasogenic edema caused by the infiltrating cells, whereas disruption of white matter tracts causes a reduction in anisotropic q component.\(^11\)

The SVZ might thus play an important role in GBM initiation and local tumor recurrence, but its diffusion imaging characteristics have been unknown. We therefore aimed to characterize the SVZ using DTI to show involvement of the SVZ in GBM. We hypothesized that the presence of tumor cells within the
SVZ leads to infiltration and disruption of white matter, with corresponding detectable alterations on DTI.

METHODS

Patient Population
We prospectively recruited patients with a supratentorial primary GBM suitable for maximal resection surgery and a World Health Organization performance scale of 0–1 between 2010 and 2014. All patients underwent standard therapy consisting of maximal safe surgical resection, followed by concomitant chemoradiotherapy and adjuvant chemotherapy. All tumors that were not GBMs in the final pathology report were excluded. All patients underwent preoperative and postoperative MRI scans. The extent of resection was classified as whether there was complete or incomplete resection of the contrast-enhancing tumor. Written informed consent was obtained from all participants and this study was approved by the local institutional review board (10/H0308/23).

MRI Acquisition
Preoperative multisequence MRI data acquisition was performed using a 3.0-Tesla Siemens MR Magnetron System (Siemens Healthcare, Munich, Germany) with a standard 12-channel head coil. Preoperative imaging included T1-weighted postcontrast imaging, a T2-weighted fluid-attenuated inversion recovery (FLAIR) sequence, and DTI (Figure 1). An anatomic three-dimensional T1-weighted sequence with fat suppression was acquired after the intravenous injection of 9 mL gadolinium (Gadovist [Bayer Schering Pharma, Berlin, Germany]) (repetition time [TR]/echo time [TE]/inversion time [TI], 2300/2.98/900 milliseconds; flip angle, 9°; field of view, 256 × 240 mm; 176–208 slices; no slice gap; voxel size, 1 × 1 × 1 mm). A two-dimensional FLAIR sequence was also acquired (TR/TE/TI, 7840–8420/95/2500 milliseconds; flip angle, 150°; field of view, 250 × 200 mm; 25–27 slices; 1-mm slice gap; voxel size, 0.78 × 0.78 × 4 mm). DTI data were obtained using a single-shot echo-planar sequence (TR/TE, 8300/98 milliseconds; flip angle, 90°; field of view, 192 × 192 mm; 63 slices; no slice gap; voxel size, 2 × 2 × 2 mm) with multiple b values (0, 350, 650, 1000, 1300, and 1600 seconds/mm²) scanned in 13 directions comparable to our previous studies.
SVZ involvement characterized by DTI in glioblastoma

Figure 1

Preoperative multisequence magnetic resonance imaging. Example of different magnetic resonance imaging modalities in a patient with a large subventricular zone contacting glioblastoma: (A) T1-weighted post-contrast imaging; (B) T2-weighted fluid-attenuated inversion recovery sequence; (C) isotropic p diffusion tensor imaging; (D) anisotropic q diffusion tensor imaging.

Data Processing
Diffusion images were processed using tools from the Oxford Centre for Functional MRI of the Brain (FMRIB) Software Library (FSL) version 5.0.0 (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/, Oxford, UK). DTI data were further decomposed into an isotropic (p) component and anisotropic (q) component. DTI and FLAIR images were coregistered with preoperative T1-weighted postcontrast images by a linear transformation using the FLIRT (FMRIB linear image registration tool) functions provided by FMRIB Software Library.

Regions of Interest
We identified the SVZ as a 5-mm margin surrounding the ventricles corresponding to earlier definitions of the SVZ used by others.15-17 Ventricle masks were created in GeoS (Microsoft Corp., Redmond, Washington, USA) from the preoperative T1-weighted postcontrast images.18 Nonenhancing FLAIR maps were generated from coregistered T2-FLAIR sequences in three-dimensional slicer (http://www.slicer.org). A normal-appearing white matter (NAWM) control was taken from the contralateral hemisphere.

We created our regions of interest (ROIs) in Matlab (MathWorks Inc., Natick, Massachusetts, USA) (Figure 2). We thus defined 4 regions: (1) The SVZ region with high FLAIR; (2) The SVZ without high FLAIR; (3) Control region of high FLAIR outside the SVZ; (4) The NAWM control
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Figure 2

Regions of interest. Regions of interest on axial T2 fluid-attenuated inversion recovery (FLAIR) imaging. (1) Subventricular zone with high FLAIR; (2) subventricular zone without high FLAIR; (3) high FLAIR control; (4) contralateral normal-appearing white matter control. CE, contrast enhancement.

Statistical Analysis
All collected data were statistically tested in SPSS version 22 (IBM Corp., Armonk, New York, USA). One-way analyses of variance with a Tukey post hoc test were used to compare the ROIs as the D’Agostino-Pearson normality test for continuous and the χ² for dichotomous data showed that all ROI data were normally distributed. A 2-sided P value of 0.05 was used for this study.

RESULTS

General Characteristics
Of the 115 initially enrolled patients, 93 met the inclusion criteria and were included in this study. The remaining 22 patients were excluded because histology showed a non-GBM tumor (n = 11), or because radiologic data were not accessible (n = 11). Patients in our cohort had a mean age of 57.6 years (range, 22–74 years) and 75% were males. General characteristics are summarized in Table 1.

Imaging Characteristics of the SVZ
One-way analysis of variance showed that all imaging parameters showed differences between the regions for all MRI parameters (isotropic [p] $F_{3,365} = 70.4; P < 0.001$; anisotropic (q) $F_{3,365} = 50.2; P < 0.001$; fractional anisotropy $F_{3,365} = 70.8; P < 0.001$) (Figure 3).
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Table 1 – General characteristics

<table>
<thead>
<tr>
<th>Descriptives</th>
<th></th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>93</td>
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<tr>
<td>Mean age, years (range)</td>
<td>57.6 (22.1–73.8)</td>
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<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>70 (75.3)</td>
</tr>
<tr>
<td>Female</td>
<td>23 (24.7)</td>
</tr>
<tr>
<td><strong>Extent of resection, n (%)</strong></td>
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</tr>
<tr>
<td>Gross total</td>
<td>48 (51.6)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>20 (21.5)</td>
</tr>
<tr>
<td>Biopsy</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Missing</td>
<td>25 (26.9)</td>
</tr>
<tr>
<td><strong>O6-methylguanine-DNA-methyltransferase status, n (%)</strong></td>
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</tr>
<tr>
<td>Methylated</td>
<td>19 (20.4)</td>
</tr>
<tr>
<td>Nonmethylated</td>
<td>30 (32.3)</td>
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<tr>
<td>Missing</td>
<td>44 (47.3)</td>
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<tr>
<td><strong>Isocitrate dehydrogenase status, n (%)</strong></td>
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<tr>
<td>Mutated</td>
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<tr>
<td>Wild-type</td>
<td>80 (86)</td>
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<td>Missing</td>
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</table>

Post hoc tests for the mean isotropic (p) DTI value (Figure 3A) of the SVZ with high FLAIR showed it to be significantly higher than the SVZ without high FLAIR ($t_{126} = 3.9; P < 0.001$), the control high FLAIR ($t_{179} = 1.9, P = 0.046$), and the control NAWM ($t_{89} = 13.7; P < 0.001$). The SVZ without high FLAIR showed significantly higher values than the control NAWM ($t_{92} = 20.4; P < 0.001$). The SVZ without high FLAIR and the high FLAIR control did not differ significantly from each other ($t_{136} = -1.6; P = 0.368$).
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Figure 3

Diffusion tensor imaging characteristics in regions of interest. Normalized diffusion tensor imaging values (A, isotropic p; B, anisotropic q; C, fractional anisotropy) in the regions of interest. 1, Subventricular zone with FLAIR (fluid-attenuated inversion recovery); 2, subventricular zone without high FLAIR; 3, high FLAIR control; 4, normal-appearing white matter. Post hoc testing identified significant differences between the groups. Level of significance is shown with asterisks: *P < 0.05; **P < 0.01; ***P < 0.001.

For the anisotropic q component (Figure 3B), the SVZ with high FLAIR showed no difference with the SVZ without high FLAIR (t156 = –0.7; P = 0.782) on post hoc testing. However, the SVZ with high FLAIR was significantly higher than the control high FLAIR (t145 = 8.2; P < 0.001) and control NAWM (t89 = 3.1; P = 0.005). The SVZ without high FLAIR was also significantly higher compared with the control high FLAIR (t181 = 11.6; P < 0.001) and control NAWM (t92 = 6.0; P < 0.001).

Mean fractional anisotropy values (Figure 3C) post hoc testing for the SVZ with high FLAIR showed significantly higher values compared with the control high FLAIR (t152 = –6.3; P < 0.001). However, it was significantly lower compared with the SVZ without high FLAIR (t154 = –3.2; P < 0.001) and control NAWM (t89 = –4.9; P < 0.001). The SVZ without high FLAIR was also significantly higher than the control high FLAIR (t184 = 12.4; P < 0.001) but was similar compared with the control NAWM (t92 = –1.6; P = 0.674).

DISCUSSION

In this study, we characterized the SVZ in relation to GBM using DTI. Our DTI data were suggestive of tumor cells infiltrating the SVZ because isotropic p values were increased in the SVZ with high FLAIR.

Mean isotropic p values in the SVZ with high FLAIR in our study showed an increase of >10% compared with the SVZ without high FLAIR signal. We have previously shown that an increase in isotropic p of >10% corresponds to infiltration by tumor cells.11 The anisotropic q values were not significantly
Reduced within the SVZ with high FLAIR, suggesting that tumor cells infiltrated, rather than disrupted, the white matter composition. This theory indicates that the tumor does not originate from the SVZ but rather grows toward it.19

Only half of GBMs may be initiated by cancer stem cells, whereas the other half arise from dedifferentiated mature glial cells, based on the anatomic location of the tumor according to Lim et al.20 Contrary to this theory, Berger et al.21 proposed that cells can, besides normal mitosis, undergo an asymmetric division. In stem cells, this theory means that the mother stem cell divides into 1 self-renewing stem cell and 1 progenitor cell, which can further differentiate. In their work, these investigators suggested that cancer stem cells reside in their niche, which clinically can be a silent area, whereas the cancer progenitor cells would migrate away from the SVZ and give rise to a tumor.21 This migratory capability of stem cells is further supported by several animal studies.6,7 Also, in humans, SVZ stem cells have been shown to be capable of producing neuroblasts that can migrate away from the SVZ to areas of injured brain tissue.22 In infarcted areas of the brain, these neuroblasts subsequently differentiated into mature neurons, which are involved in brain repair mechanisms after injury. These studies suggest that SVZ stem cells could migrate to more cortical areas of the brain and initiate GBM distant from the SVZ. We therefore did not correct for the anatomic location of the tumor in the current study.

Because GBMs extend outside the outer enhancing ring on conventional MRI, infiltrating tumor cells can be found within the peritumoral high FLAIR signal, although this can be mixed with vasogenic edema effects. To overcome the limitations of conventional FLAIR imaging, more advanced MRI methods can be used in combination to show the invasive margin of GBM outside the contrast enhancement. Contrary to what would be expected in the peritumoral invasive margin, the high FLAIR control in this study did not show significantly higher isotropic p values compared with the SVZ without high FLAIR. Partial volume effects of the cerebral spinal fluid are known to increase isotropic diffusion measures, which possibly explains this finding.23 This theory is further supported by the anisotropic q values, because the high FLAIR control showed significantly lower values compared with the other regions. Our high FLAIR control showed a reduction in anisotropic q value of >21%, well above the threshold of 12% that we previously used to identify disruption of white matter.11,14

Limitations
A limitation of this study is that the diffusion changes are not specific for tumor infiltration but can also represent edema. Histologic data are not available for
our current study. However, we previously histologically validated that these diffusion changes correspond to tumor infiltration.\textsuperscript{11}

CONCLUSIONS

This study is the first to characterize the SVZ in GBM using diffusion imaging. Because DTI-derived isotropic p values were increased in an area of the SVZ, suggestive of tumor infiltration, we propose that the SVZ is involved in GBM.
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