Correlation between Tumor Location and Clinical Properties of Glioblastomas in Frontal and Temporal Lobes

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BACKGROUND: Tumor location is a major prognostic factor in glioblastoma and may associate with clinical properties. The present study established and analyzed the correlation between tumor location and clinical properties of glioblastomas in frontal and temporal lobes.

METHODS: This retrospective study determined the location of glioblastoma, frontal lobe (FL) or temporal lobe (TL), based on preoperative MR images. The glioblastomas in FL at clinical, radiological, and molecular levels were explored to define their clinical properties, including gender, age, sides, relationship to the ventricle, imaging subtypes, volumetrics, IDH mutation, promoter methylation of MGMT, PFS and OS as compared to glioblastomas in TL.

RESULTS: A total of 406 patients were enrolled: 182 (44.83%) and 224 (55.17%) in FL and TL groups, respectively, with a mean age of 69.8 years. Compared to FL, TL had a higher incidence of female patients ($P=0.024$), distant to the ventricle ($P=0.006$), IDH mutation ($P=0.021$), promoter methylation of MGMT ($P=0.012$), and prolonged PFS and OS ($P=0.05$) in glioblastomas patients. No significant differences were observed with respect to age $\geq 60$y at study entry ($P=0.668$), sides ($P=0.879$), imaging subtypes ($P=0.362$), or volumetrics ($P=0.709$) between the two groups.

CONCLUSIONS: This study demonstrated that different tumor locations are associated with diverse clinical properties of glioblastoma in FL and TL. This would aid in increasing our understanding of glioblastoma biology for application in baseline comparisons in future clinical trials.

Key words: Glioblastomas; Tumor location; Clinical Properties


INTRODUCTION

Glioblastoma, classified as World Health Organization (WHO) grade IV, is the most common malignant brain tumors in adults with an incidence rate of 23 per 100,000 persons¹. One of the key features of glioblastoma is their dispersive, infiltrative nature, which makes visualization of the tumor difficult². The standard therapy options include maximally safe neurosurgical resection³, radiotherapy, and chemotherapy preferentially using the alkylating drug temozolomide, along with antiangiogenic treatment using the antibody bevacizumab, and controlled symptoms through corticosteroids for increased intracranial pressure, anticonvulsants and best supportive care³. Despite recent advances in surgery, radiotherapy, and chemotherapy, the prognosis of glioblastoma is yet extremely poor. Patients only have a median survival of 12-18 months after initial diagnosis,
and resistance to current therapeutic approaches is a major cause of clinical deterioration\textsuperscript{6,7}. Young age and superior preoperative Karnofsky Performance Status score, MGMT promoter methylation, and loss of 19q might be prognostic for a prolonged survival of glioblastomas patients\textsuperscript{6}.

Several studies revealed that tumor location was a significant prognostic factor associated with tumorigenesis and tumor-specific genetic changes. For instance, 1p/19q co-deletion was found to occur predominantly in frontal lobe (FL) glioblastomas\textsuperscript{9}. Supratentorial ependymomas had a significantly poor progression-free survival (PFS) and overall survival (OS) than their infratentorial counterparts, according to the reports by Sayegh et al\textsuperscript{10}. Although tumor location is a major clinical factor, the correlation between tumor location and clinical properties of glioblastomas in frontal and temporal lobes is yet ambiguous.

Thus, in order to increase our understanding of glioblastoma biology, investigating the correlation between tumor location and clinical properties of glioblastomas is essential. Herein, we investigated the parameters such as gender, age, sides, relationship to the ventricle, imaging subtypes, volumetrics, IDH mutation, promoter methylation of MGMT, PFS and OS at clinical, radiological, and molecular levels from a large cohort of patients, who underwent surgery for intracranial glioblastomas in FL to create statistical atlases as compared to glioblastomas in temporal lobe (TL).

METHODS

Study Population

After obtaining the Institutional Ethics Board approval and written consent from all enrolled patients, we retrospectively reviewed the clinical and follow-up data of 406 patients with newly diagnosed, pathology-proven glioblastomas in FL and TL, who underwent craniotomy for tumor resection at the Department of neurosurgery, the Second Affiliated Hospital of Zhejiang University School of Medicine from August 2011 to August 2017. The neuropathological diagnosis was confirmed by examination of the tumor specimen by two independent neuropathologists, blinded to the patients’ other clinical information according to the criteria established by the World Health Organization\textsuperscript{11}.

Patients with solitary glioblastomas were included if they fulfilled the following criteria: (1) primary glioblastomas in FL or TL; (2) aged $>18$y and had presurgical MR images; (3) no prior craniotomy or biopsy; (4) underwent operation $\leq 2$ weeks after primary diagnosis and pathological confirmation of glioblastoma; (5) no history of radiotherapy or chemotherapy; (6) underwent gross total resection that was defined as $>95\%$ of the area with abnormal T2 hyperintensity before surgery. The exclusion criteria were as follows: (1) no histological diagnosis available; (2) multilobar or bilateral; (3) recurrence of glioblastomas or location in the spinal cord; (4) three neuroradiologists had different opinion about tumor location, relationship to ventricle, or imaging subtypes; (5) two neuropathologists had different opinion about neuropathological diagnosis; (6) secondary glioblastoma; (7) lack of gross total resection.

All patients underwent safe resection and radiotherapy plus chemotherapy with temozolomide, according to standard of care. The tumor locations, relationship to the ventricle, imaging subtypes, and volume of glioblastoma were evaluated and validated based on a consensus opinion of a panel of three neuroradiologists with extensive experience in neuro-oncology blinded to the other clinical information at our institutions. The clinical information, which included the location of glioblastoma, gender, age, sides, relationship to the ventricle, imaging subtypes, volumetrics, IDH mutation, promoter methylation of MGMT, PFS and OS were collected retrospectively for statistical analysis.

Tumor Locations and Relationship to Ventricle
Tumor location (FL or TL) was determined based on T1-weighted MR images, FLAIR, T2-weighted MR images after gadolinium-based contrast administration. If a patient underwent more than one MR scan, the first scan that displayed the tumor was used in this study. To simplify the analysis, tumors were localized according to their geometric center, following which, the lobar location was determined (Figure 1).

As described previously in the literature, relationship to ventricle was estimated according to the distance of the contrast-enhancing margins of glioblastomas to ventricle on preoperative contrast MR images. The tumors were considered close to the ventricle if the shortest distance to a ventricle was ≤ 10 mm, including involvement of the ventricle system if the contrast-enhancing lesions contacted the lining of the ventricle, and considered distant to the ventricle if the distance was > 10 mm.

**Imaging Subtypes and Volumetric**

According to the study conducted by Itakura et al, three distinct imaging subtypes (outline of the tumor boundary) “clusters” — pre-multifocal, spherical, and rim-enhancing, reflecting their imaging characteristics — were manually delineated according to MR contrast images, as shown in Figure 2.

Tumor volume was defined as the pathological contrast enhancement plus the necrotic tissue within the contrast enhancing borders. Whole-brain post-contrast T1-weighted and T2/FLAIR images from MRI were used for tumor volume segmentation. All tumor segmentations were done using 3D Slicer software, version 4.1 (3D Slicer; https://www.slicer.org/), as previously reported. User-driven manual active contour segmentation was used to acquire the volume quantification for the regions of interest in the enhanced tumor target as well as T2/FLAIR abnormalities.

**DNA extraction and molecular evaluation**

All tumor specimens were snap frozen upon surgical resection and preserved at −80°C until use. Tumor specimens containing 20% or more non-tumor tissue or necrotic areas were excluded from further analysis. Genomic DNA was isolated from the frozen tumor tissues using the QIAamp DNA Mini Kit (Qiagen) according to the manufacturer’s protocol. The DNA concentration and quality were measured using the Nano-Drop ND-1000 spectrophotometer (NanoDrop Technologies, Houston, TX, USA). The IDH mutations, including mutation hotspots in codon 132 of IDH1 and codon 172 of IDH2, were assessed by pyrosequencing, as previously described. The MGMT promoter methylation status was determined by methylation-specific PCR and evaluated as reported.

**PFS and OS**

PFS was defined as the time from surgery to tumor progression observed on post contrast MR images. OS was calculated as time from surgery to death. The overall follow-up duration ranged from August 2011 to August 2017 in our study.

**Statistical analysis**

All statistical analyses were performed using SPSS version 21.0 (SPSS Institute, Chicago, USA). A Student t test was used to compare differences for continuous data which are expressed as mean ± standard deviation (SD).
Other clinical variables were evaluated using \( \chi^2 \) test and Fisher’s exact test. The patient PFS and OS were calculated using the Kaplan–Meier method, and were compared using the log-rank test. A two-tailed \( P < 0.05 \) was considered significant.

**RESULTS**

**Clinical Features**

As shown in Table 1, a total of 406 patients, including glioblastomas in FL 182 (44.83%) and TL 224 (55.17%), with a mean age of 69.8 y, fulfilled the study criteria. The FL group males had a significantly higher incidence than those with TL location (57.69% versus 47.32%, respectively), while female patients in TL had a slightly higher incidence than in FL (52.68% versus 42.31%, respectively, \( P=0.024 \)). The incidence of age \( \geq 60 \text{y} \) at the time of participation in FL group was slightly higher compared to TL, albeit without no statistical difference (\( P=0.668 \)). Glioblastomas proximal to the ventricle in FL showed a statistically greater incidence as compared to TL (66.48% versus 53.13%, respectively, \( P=0.006 \)). However, no statistical differences were observed regarding the sides (\( P=0.879 \)), imaging subtypes (\( P=0.362 \)), or volumetrics (\( P=0.709 \)).

**Molecular Evaluation**

Table 2 and Figure 3 summarized the baseline characteristics about the molecular evaluation of the two study groups. All patients had IDH mutation status and MGMT promoter methylation data available; 28(6.90%) glioblastomas harbored IDH mutations, and 276(65.52%) showed MGMT promoter methylation. Statistical differences were noted in the type of IDH (\( P=0.021 \)) and promoter methylation of MGMT (\( P=0.012 \)) between the two groups. The IDH mutation and promoter methylation of MGMT had a significantly higher incidence in TL than FL (9.38% versus 3.85%, 70.53% versus 59.34%, respectively).

**PFS and OS analysis**

At a median follow-up time of 16 months (range, 10-25 months), the median PFS was 9 months and median OS was 15 months. The median PFS was 9 months in FL and 10 in TL, while median OS was 14 months in FL and 17 in TL. Furthermore, Kaplan–Meier analysis and Cox regression showed a significant difference in the PFS between glioblastomas in FL and TL (\( P<0.05 \), Figure 4). These analyses also demonstrated that glioblastomas in FL had a significantly worse outcome of OS as compared to those in TL (\( P<0.05 \), Figure 5).

**DISCUSSION**

Glioblastoma is the most common brain and central nervous system malignancy, accounting for 54% of all gliomas, 45.2% of primary malignancies in the brain, and 16% of all primary brain tumors. Despite research and improvement in treatments modalities, the prognosis of glioblastoma remains poor, and its biology is yet to be elucidated.
The treatment of brain tumor based on the surgical and chemotherapeutic guidelines are mostly dependent of tumor location. Evidence suggests that tumor location might be linked to the genetic profile of tumor cells with respect to the origin and region that has been identified in oligodendrogliomas\textsuperscript{20-22} and ependymomas\textsuperscript{23}. Owing to the significant impact on patient outcomes and the incomplete physiological characterization, an in-depth understanding of the underlying clinical properties is essential. In this study, we attempted to investigate the clinical properties of glioblastomas in the frontal and temporal lobes at clinical, radiological and molecular levels in order to increase our understanding of glioblastoma biology.

The FL group males had a significantly higher incidence than those with TL location (57.69\% versus 47.32\%, respectively), while female patients in TL had a slightly higher incidence than in FL (52.68\% versus 42.31\%, respectively, \(P=0.024\)) in the current study. The difference in location observed between genders may be credited to hormonal physiology\textsuperscript{24}. The incidence of age \(\geq 60\) y at study entry in the FL group was slightly higher compared to TL, albeit without a statistical difference (\(P>0.05\)). However, according to Wang et al\textsuperscript{25}, the increased frequency of temporal lobe glioblastoma among patients with advanced age, was not identical. Neither sides nor volumetrics showed a statistical difference between the two groups (\(P > 0.05\)); however, the main reasons were not yet completely understood. Bilello et al\textsuperscript{26} found that differences in spatial maps of tumor size putatively correlated to the function of surrounding cortex and tumors in eloquent areas of the brain, which might be symptomatic and prompt earlier medical attention as compared to similar sized tumors in non-eloquent regions.

Relationship to ventricle was also revealed as a useful predictor that associated with tumor-specific changes in glioblastomas. Recent studies demonstrated that patients with glioblastoma location close (\(\leq 10\) mm) to the ventricle system exhibited a rapid progression and decreased PFS and OS\textsuperscript{8,12,25,27}. The aggressive behavior of the specific subtypes of glioblastomas may be related to the recruitment of neural stem cells from the subventricular zone that display a propensity for invasive proliferation\textsuperscript{20}. The current study found that glioblastomas closed to the ventricle in FL showed a significantly greater incidence as compared to TL (\(P=0.006\)). However, no statistical difference was noted in the imaging subtypes between FL and TL (\(P>0.05\)); the association of tumor location with specific image-based clusters remains unknown.

IDH mutations, one of the molecular biomarkers of glioblastoma, result in the loss of native enzymatic activity as well as exhibit novel activity during the production of 2-hydroxyglutarate. These enzymatic alterations ultimately trigger epigenetic changes that defined the glioma CpG island methylation phenotype\textsuperscript{28-30}. IDH mutations are considered as favorable prognostic factors, accounting for 5-12\% of all primary glioblastomas\textsuperscript{30}. In the present study, the IDH mutation in TL group had a significantly higher incidence than the FL group (9.38\% versus 3.85\%, \(P=0.021\)).

Although nitrosoureas were commonly used for chemotherapy, temozolomide is now used for first-line therapy. The cytotoxic effects of temozolomide are mediated by DNA methylation at the O\textsuperscript{6}position of guanine as well as by an intact DNA mismatch repair pathway. The DNA repair protein MGMT repairs O\textsuperscript{6}-methyl adducts in DNA, rendering it as a critical regulator of the cytotoxic effects of temozolomide\textsuperscript{31}. Hypermethylation of the MGMT promoter region can silence its expression and result in a deficiency in MGMT-mediated DNA repair, which is associated with improved survival in glioblastomas patients treated with alkylating agents such as temozolomide\textsuperscript{31}. Herein, the promoter methylation of MGMT in TL had a significantly higher incidence than FL (70.53\% versus 59.34\%, \(P=0.012\)).

Various clinical trials have postulated that IDH mutation and MGMT promoter methylation associate with prolonged PFS and OS in glioblastomas patients\textsuperscript{32-34}. The present study demonstrated that IDH mutation and promoter methylation of MGMT in TL had a significantly higher incidence than FL. Several studies proved that glioblastomas close to ventricle were associated with decreased PFS and OS\textsuperscript{8,12,25,27}. The glioblastomas close to the ventricle in FL showed a statistically higher incidence as compared to TL in our study. Thus, it is can be
hypothesized that the PFS and OS of patients were significantly longer in TL than FL. This article further showed that glioblastomas in TL presented a significantly better outcome of PFS and OS as compared to FL \((P<0.05)\) in agreement with this hypothesis.

The results from the current study suggested that different tumor locations were consistent with various clinical properties of glioblastomas in FL and TL. Compared to FL, TL had a higher incidence of female patients, distant to the ventricle, IDH mutation, promoter methylation of MGMT, and prolonged PFS and OS in glioblastomas patients. No significant differences were observed with respect to age \(\geq60\)y at the time of participation, sides, imaging subtypes, or volumetrics between the two groups. The restricted patterns in topographic distribution of glioblastomas appear to arise from specific phenotypes, which appear consistent with the hypothesis of distinct glioma cells of origin; however, the underlying mechanisms are yet to be elucidated.

Owing to the retrospective design of the study, the current results are subject to the bias inherent of a non-randomized, retrospective study. There are four particular limitations that warrant further discussion. One of the limitations of this study stems from the evaluated and validation of tumor distribution, relationship to the ventricle, and imaging prototypes of glioblastomas were according to the consensus of a panel of three neuroradiologists; it was often challenging to extract objective information for scientific analysis from the statements describing the imaging features. Second, no pediatric patients were included in the study. Third, we used only contrast enhancement as a putative marker of glioblastomas as the non-enhancing areas of edema, and the normal-appearing brain may contain glioblastomas. Fourth, the study included a relatively low number of patients, which might have weakened the statistical power of the study. Therefore, further studies with larger sample cases are necessary to confirm these findings.

**CONCLUSION**

Based on preoperative MR images and relevant clinical data from a large cohort of patients with primary diagnosis of glioblastomas, our results demonstrated that tumor location is a major factor, and glioblastomas in FL and TL have different clinical properties. Compared to the FL, TL had a higher incidence of female patients, distant to the ventricle, IDH mutation, promoter methylation of MGMT, longer PFS and OS in glioblastomas patients. Therefore, the findings of this study would increase our understanding of glioblastoma biology.

**ACKNOWLEDGMENTS**

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**REFERENCES**


Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.
### Table 1. General Characteristics of the Two Study Groups (n [%])

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Frontal Lobe (FL) (n=182)</th>
<th>Temporal Lobe (TL) (n=224)</th>
<th>P Value</th>
</tr>
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<tr>
<td>Gender</td>
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<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>105 (57.69)</td>
<td>106 (47.32)</td>
<td>$X^2=4.327, P=0.024$</td>
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<tr>
<td>Female</td>
<td>77 (42.31)</td>
<td>118 (52.68)</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;60y</td>
<td>28 (15.38)</td>
<td>38 (16.96)</td>
<td>$X^2=0.184, P=0.668$</td>
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<tr>
<td>≥60y</td>
<td>154 (84.62)</td>
<td>186 (83.04)</td>
<td></td>
</tr>
<tr>
<td>Sides</td>
<td></td>
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<tr>
<td>Left</td>
<td>101 (55.49)</td>
<td>126 (56.25)</td>
<td>$X^2=0.023, P=0.879$</td>
</tr>
<tr>
<td>Right</td>
<td>81 (44.51)</td>
<td>98 (43.75)</td>
<td></td>
</tr>
<tr>
<td>Relationship to Ventricle</td>
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<td>Close</td>
<td>121 (66.48)</td>
<td>119 (53.13)</td>
<td>$X^2=7.414, P=0.006$</td>
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<tr>
<td>Distant</td>
<td>61 (33.52)</td>
<td>105 (46.87)</td>
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<tr>
<td>Pre-Multifocal</td>
<td>82 (45.06)</td>
<td>99 (44.20)</td>
<td>$X^2=2.034, P=0.362$</td>
</tr>
<tr>
<td>Spherical</td>
<td>64 (35.16)</td>
<td>91 (40.63)</td>
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<tr>
<td>Rim-Enhancing</td>
<td>36 (19.78)</td>
<td>34 (15.17)</td>
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<tr>
<td>Volumetrics (cm$^3$)</td>
<td>129.9±73.4</td>
<td>135.8±79.9</td>
<td>$P=0.709$</td>
</tr>
<tr>
<td>Molecular Evaluation</td>
<td>Frontal Lobe (n=182)</td>
<td>Temporal Lobe (n=224)</td>
<td>P Value</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td><strong>IDH</strong></td>
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<td></td>
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</tr>
<tr>
<td>Wild</td>
<td>175(96.15)</td>
<td>203(90.62)</td>
<td>$X^2=4.780$, $P=0.021$</td>
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<tr>
<td>Mutation</td>
<td>7(3.85)</td>
<td>21(9.38)</td>
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<td><strong>MGMT</strong></td>
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<tr>
<td>Methylated</td>
<td>108(59.34)</td>
<td>158(70.53)</td>
<td>$X^2=5.570$, $P=0.012$</td>
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<tr>
<td>Unmethylated</td>
<td>74(40.66)</td>
<td>66(29.47)</td>
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</tr>
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Figure 1. The MR contrast images of glioblastomas. The preoperative (A) and postoperative (B) enhanced MRI images of a patient with glioblastoma in FL. The preoperative (C) and postoperative (D) enhanced MRI images of a patient with glioblastoma in TL.
Figure 2: Three distinct imaging subtypes — pre-multi-focal, spherical, and rim-enhancing according to MR contrast images.
Figure 3. The baseline characteristics of the molecular evaluation of the two study groups. IDH mutation and promoter methylation of MGMT had a significantly higher incidence in TL than FL (9.38% versus 3.85%, 70.53% versus 59.34%, respectively, \( P < 0.05 \)).
Figure 4. The median PFS was 9 months in FL and 10 in TL. Kaplan–Meier analysis and Cox regression showed that glioblastomas in FL had a significantly worse outcome of PFS as compared to those in TL (P<0.05).
Figure 5. The median OS was 14 months in FL and 17 in TL. Kaplan–Meier analysis and Cox regression demonstrated that glioblastomas in FL had a significantly worse outcome of OS as compared to those in TL (P<0.05).
Highlights

- We compiled MR images from patients with glioblastoma in frontal lobe (FL) and temporal lobe (TL).
- The FL group males had a significantly higher incidence than those with TL location, while female patients in TL had a slightly higher incidence.
- The incidence of age $\geq$60y at the time of participation in FL group was slightly higher compared to TL, albeit without statistical difference.
- Glioblastomas proximal to the ventricle in FL showed a statistically greater incidence as compared to TL.
- No statistical differences were observed regarding the sides, imaging subtypes, or volumetrics.
- The IDH mutation and promoter methylation of MGMT had a significantly higher incidence in TL than FL.
- Kaplan–Meier analysis and Cox regression showed that glioblastomas in TL had a better outcome of PFS at a statistically significant level, compared with glioblastomas in FL.
- Kaplan–Meier analysis and Cox regression showed that glioblastomas in TL had a better outcome of OS at a statistically significant level, compared with glioblastomas in FL.
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