Putamen involvement and survival outcomes in patients with insular low-grade gliomas

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OBJECTIVE Insular glioma has a unique origin and biological behavior; however, the associations between its anatomical features and prognosis have not been well established. The object of this study was to propose a classification system of insular low-grade gliomas based on preoperative MRI findings and to assess the system’s association with survival outcome.

METHODS A total of 211 consecutively collected patients diagnosed with low-grade insular gliomas was analyzed. All patients were classified according to whether tumor involved the putamen on MR images. The prognostic role of this novel putaminal classification, as well as that of Yaşargil’s classification, was examined using multivariate analyses.

RESULTS Ninety-nine cases (46.9%) of insular gliomas involved the putamen. Those tumors involving the putamen, as compared with nonputaminal tumors, were larger (p < 0.001), less likely to be associated with a history of seizures (p = 0.04), more likely to have wild-type IDH1 (p = 0.003), and less likely to be totally removed (p = 0.02). Significant favorable predictors of overall survival on univariate analysis included a high preoperative Karnofsky Performance Scale score (p = 0.02), a history of seizures (p = 0.04), gross-total resection (p = 0.006), nonputaminal tumors (p < 0.001), and an IDH1 mutation (p < 0.001). On multivariate analysis, extent of resection (p = 0.035), putamen classification (p = 0.014), and IDH1 mutation (p = 0.026) were independent predictors of overall survival. No prognostic role was found for Yaşargil’s classification.

CONCLUSIONS The current study’s findings suggest that the putamen classification is an independent predictor of survival outcome in patients with insular low-grade gliomas. This newly proposed classification allows preoperative survival prediction for patients with insular gliomas.

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KEY WORDS classification; insular glioma; prognosis; putamen; oncology

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The insular lobe is an anatomical structure located in the depth of the sylvian fissure, overlying the basal ganglia block and hidden by the opercula of the frontal, parietal, and temporal lobes.4,28,29,36 Its origin from the mesocortex, which connects the allocortex and neocortex, means that the insula has complex afferent and efferent connections to and from the surrounding structures, such as the limbic system, thalamus, basal ganglia, and internal capsule.1,12,18

The insular area is a predilection site for gliomas,34,37 with insular gliomas accounting for up to 25% of low-grade gliomas (LGGs) and 10% of high-grade gliomas.5–7 Given the complexity of the insular anatomy and their origin, insular gliomas have unique biological behaviors, and patients harboring these lesions are more likely to show a slowly progressive disease course than those with gliomas located in other regions of the brain.23

Several classifications of insular tumors have been suggested to better describe the anatomy of these tumors. These classifications were based on the fasciculi,16 vasculature,17 anatomical relationship,5,23 and invasive trends.19,21,34–37,39 However, little is currently known about the associations between these classifications of insular gliomas and survival outcomes. In fact, only a single study24 has suggested that a Yaşargil Type 5A/B tumor with frontal extension is a significant predictor of survival. However, since this con-
clusion was made for tumors of all grades (WHO Grades I–III), potential bias caused by inconsistencies in the grade of malignancy should be considered.

In the current study, we collected a consecutive cohort of insular LGGs and proposed a novel anatomically based tumor classification, which we suggest can play a role in predicting survival outcomes.

Methods

Patient Characteristics

In this study we collected data on 250 consecutive patients with primary insular glioma surgically treated at our institute in the period from July 2006 to June 2012. Patients were enrolled in the study if they met the following criteria: 1) age ≥ 16 years, 2) presurgical MRI available, and 3) pathologically confirmed diffuse LGG (WHO Grade II). Thirty-nine patients were excluded because of a previous diagnosis of brain tumor or a previous biopsy or because postoperative MRI studies (within 72 hours) were not available.

Two independent neuroradiologists blinded to all patients’ clinical information confirmed the histological diagnosis. Tumors were volumetrically analyzed by measuring hyperintense regions on axial T2-weighted MR images. Extent of resection was assessed by comparing the volumes of pre- and postsurgery T2 hyperintensity and was classified as gross total (> 90%), subtotal (70%–90%), or partial (< 70%) to ensure consistency between this study and previous studies that focused on the prognostic impact of glioma resections.11,19,22–26 Patients’ clinical data were collected from the institutional medical records. This study was approved by our institutional review board, and written consent was obtained from all enrolled patients.

Magnetic Resonance Imaging Data Collection

Magnetic resonance imaging studies were performed using a Siemens Trio 3-T scanner (Siemens Healthcare), typically including the following sequences: 1) axial T1-weighted images, TR 450 msec, TE 15 msec, section thickness 5 mm; 2) T2-weighted images, TR 6000 msec, TE 140 msec, section thickness 5 mm; and 3) postcontrast T1-weighted images using gadopentetate dimeglumine injection (0.1 mmol/kg, Beilu Pharma), TR 450 msec, TE 15 msec, section thickness 5 mm, matrix size 256 × 256. The radiological parameters of the postoperative MR images were maintained in accordance with the preoperative scans.

Tumor Classification

We proposed a new classification of insular gliomas, the “putamen classification,” to describe the anatomical features of the tumors. In this classification, insular gliomas were divided into 2 cohorts based on whether the ipsilateral putamen was involved by the tumor on preoperative MR images (Fig. 1). The lateral edge of the putamen can be clearly seen in tumors not involving the putamen, whereas the edge can hardly be recognized in tumors involving the putamen. Two experienced neuroradiologists blinded to the patients’ clinical and pathological information typed the insular gliomas using this classification. A third senior neuroradiologist reexamined the MR images and determined the classification in each case in which inconsistency existed between the 2 neuroradiologists. In addition, all insular gliomas were classified according to Yaşargil’s classification system. The prognostic roles of the 2 different classification systems were compared using survival analyses.

IDH1 Mutation Detection

All selected samples contained at least 80% of the tumor. The genomic region spanning wild-type R132 of isocitrate dehydrogenase 1 (IDH1) was analyzed via pyrophosphate sequencing using the following primers: 5′-GCTTTGTAGTGTTGTTGAAAAAC-3′ and 5′-biotiTTGCCAACATGACTTACTTNGATC-3′. The polymerase chain reaction (PCR) analysis was performed in duplicate in 40 µl of reaction volume containing 1 µl of 10 µM of each forward and reverse primer, 4 µl of 10× buffer, 3.2 µl of 2.5-µM deoxynucleotide triphosphates, 2.5 U hotstart Taq (Takara), and 2 µl of 10-µM DNA. The PCR conditions were as follows: 95°C for 3 minutes; 50 cycles of 95°C for 15 seconds, 56°C for 20 seconds, 72°C for 30 seconds; and 72°C for 5 minutes (Applied Biosystems PCR system 9700). Single-stranded DNA was purified from the total PCR products and subjected to pyrosequencing on a PyroMark Q96 ID system (QIAGEN) using the primer 5′-TGGATGGTTAAACCT-3′ and an EpiTect Bisulfite Kit (QIAGEN).

Statistical Analysis

The chi-square test and t-test were performed for statistical comparisons of categorical variables between the 2 cohorts identified via the putamen classification. The Kaplan-Meier method and log-rank test were used to compare the survival rates between patients with the different types of insular gliomas. Univariate and multivariate Cox regression analyses were performed to determine the effects of different variables on patient survival outcomes. Progression-free survival (PFS) was defined as the time from primary surgery to an unequivocal increase in tumor size on MRI.23 Overall survival (OS) was defined as the...
time from primary surgery to death. A $p < 0.05$ was considered statistically significant.

**Results**

**Patient Demographics**

The clinical characteristics of the 2 cohorts of glioma patients classified by putaminal involvement are summarized in Table 1. Among the 211 patients included in this study, there were 123 males and 88 females, with a median age of 38 years (range 16–66 years). Preoperative seizures occurred in 120 patients (56.9%). Histopathological examination confirmed that there were 34 oligodendrogliomas (16.1%), 95 astrocytomas (45.0%), and 82 oligoastrocytomas (38.9%) in the entire cohort. Gross-total resection was achieved in 81 cases (38.4%). Ninety-nine gliomas were identified as involving the putamen, and the other 112 gliomas had no putaminal involvement.

A comparison of the clinical characteristics between the 2 lesion types revealed that putaminal tumors were larger than nonputaminal ones ($p < 0.001$), while a greater extent of resection was more likely to be achieved in nonputaminal tumors ($p = 0.02$). Interestingly, the incidence of preoperative seizures was higher in nonputaminal than putaminal tumors ($p = 0.04$). Further, tumors with wild-type IDH1 were more likely to involve the putamen ($p = 0.003$). There were no significant differences with regard to age, sex, lesion side, Karnofsky Performance Scale (KPS) score, and histopathology between the 2 cohorts. In oligodendrial gliomas, the 1p/19q codeletion was found to be associated with nonputaminal involvement ($p = 0.003$; Table 1).

**Univariate and Multivariate Survival Analyses**

Follow-up data were available in 150 patients. The mean follow-up among survivors was 56.5 months. Kaplan-Meier estimates of OS and PFS are shown in Fig. 2. In the univariate analyses, the significant predictors for a longer PFS included preoperative KPS score $\geq 90$ ($p = 0.007$), exten- sive resection ($p = 0.008$), nonputaminal tumor ($p < 0.001$), and IDH1 mutation ($p < 0.001$; Table 2). The clinical indicators associated with a longer OS included a history of preoperative seizures ($p = 0.04$), preoperative KPS score $\geq 90$ ($p = 0.02$), extensive resection ($p = 0.006$), nonputaminal tumor ($p < 0.001$), and IDH1 mutation ($p < 0.001$).

In the multivariate Cox regression analysis, extent of resection ($p = 0.025$, HR 1.62), putamen involvement status ($p = 0.003$, HR 2.49), and wild-type IDH1 ($p = 0.001$, HR 2.60) were identified as independent predictors of PFS (Table 3). Similarly, extent of resection ($p = 0.035$, HR 1.67), putamen involvement status ($p = 0.014$, HR 2.44), and wild-type IDH1 ($p = 0.026$, HR 2.12) were also identified as independent predictors of OS.

**Survival Analysis Using Yaşargil’s and Berger-Sanai’s Classifications**

Survival analysis was also performed to compare the survival outcomes between patient cohorts classified according to Yaşargil’s classification of insular gliomas,\textsuperscript{27} which is based on the anatomical location of the tumor. Kaplan-Meier analysis showed that there were no signifi-

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonputaminal Tumor</th>
<th>Putaminal Tumor</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>112</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td>Median age in yrs (range)</td>
<td>39 (16–66)</td>
<td>37 (22–63)</td>
<td></td>
</tr>
<tr>
<td>No. of patients w/ age $\geq$ 40 yrs</td>
<td>55</td>
<td>37</td>
<td>0.09</td>
</tr>
<tr>
<td>Male sex</td>
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<td>56</td>
<td>0.63</td>
</tr>
<tr>
<td>Seizure history</td>
<td>71</td>
<td>49</td>
<td>0.04</td>
</tr>
<tr>
<td>MRI features</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Table 1. Summary of clinical characteristics in 211 patients with insular tumors

\textsuperscript{*} Boldface type indicates significance.

† Result of t-test.

‡ Only 171 tumors.

§ Tested in tumors with an oligodendrial component (49 tumors).


dant differences in PFS ($p = 0.49$) and OS ($p = 0.98$) between the cohorts (Fig. 2).

The prognostic value of Berger-Sanai’s classification\textsuperscript{22} in patients with low-grade insular gliomas was also evaluated. There were no significant differences in patient survival outcomes among Berger-Sanai groups of insular gliomas ($p = 0.35$ for both PFS and OS; Fig. 3).

**Discussion**

Previous studies have proposed several classifications for insular gliomas, although most focused on the anatomical location of the tumor. The present study proposed a new classification of insular gliomas—the putamen classification, which is based on the tumor invasion on preoperative MR images. A multivariate analysis was performed in a large cohort to determine the prognostic role of this novel classification in patients with insular LGGs.

Several classifications have been proposed to describe the anatomical features of insular gliomas. Originally, Yaşargil\textsuperscript{24–37} categorized the tumors involved in the limbic and paralimbic systems based on the tumor locations on preoperative MR images. This classification was improved...
by considering the tumor developmental approach. In addition, paralimbic LGGs were classified based on the main fasciculi that the tumor invaded, whereas the anatomical relationship between the tumor and the lenticulostriate arteries was used to stratify insular gliomas in a later study. Recently, Sanai et al. proposed a quadrant-style classification of the insula, which could be used in surgical planning for insular gliomas.

The classification proposed in the current study is based on the involvement of anatomical structures of the insular area. The insular cortex faces laterally and forms the medial wall of the operculoinsular compartment. The gray matter structures that lie medial to the insular cortex include the claustrum and the putamen, both of which are generally easy to recognize on MR images obtained in healthy subjects. As the claustrum is closely adjacent to the insular cortex and has a weak structure with a slim shape, it is difficult to identify the claustrum on MR images when tumors are present. On the other hand, the putamen is a nucleus of basal ganglia that lies medial to the claustrum. As the putamen generally has a strong structure and a long arched exterior margin opposing the entire insular cortex, it can resist glioma involvement. On MR images, some insular gliomas are limited laterally to the putamen and show clear tumor boundaries, whereas others appear to invade the putamen, even involving the internal capsule. In the current study, we assumed that the tumors invading the putamen had a stronger biological capability of invasion, and we further examined this hypothesis by assessing the

\[
\text{TABLE 2. Univariate analyses of survival outcomes in 150 patients with insular gliomas*}
\]

<table>
<thead>
<tr>
<th>Factor</th>
<th>p Value, PFS</th>
<th>p Value, OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.10</td>
<td>0.42</td>
</tr>
<tr>
<td>Sex</td>
<td>0.60</td>
<td>0.86</td>
</tr>
<tr>
<td>History of preop seizures</td>
<td>0.17</td>
<td>0.04</td>
</tr>
<tr>
<td>Preop KPS score</td>
<td>0.007</td>
<td>0.02</td>
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<tr>
<td>Side</td>
<td>0.43</td>
<td>0.16</td>
</tr>
<tr>
<td>Lesion size</td>
<td>0.05</td>
<td>0.48</td>
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<tr>
<td>Putamen involvement status</td>
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<td>&lt;0.001</td>
</tr>
<tr>
<td>Histopathology</td>
<td>0.40</td>
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</tr>
<tr>
<td>Extent of resection</td>
<td>0.008</td>
<td>0.006</td>
</tr>
<tr>
<td>Yaşargil’s classification</td>
<td>0.49</td>
<td>0.98</td>
</tr>
<tr>
<td>Berger-Sanai’s classification</td>
<td>0.35</td>
<td>0.35</td>
</tr>
<tr>
<td>IDH1 states</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Boldface type indicates significance.
role of putamen involvement in determining the survival outcomes of patients with insular LGGs.

Some clinical characteristics were shown to differ between the 2 cohorts of patients according to the putamen classification. Gliomas involving the putamen were larger and less likely to be gross totally resected. As the putamen is located near the internal capsule and lenticulostriate artery, which are important structures that should be carefully preserved during surgery, resection is limited for gliomas involving the putamen.\textsuperscript{13,17,30}

Seizure is the most common symptom of insular gliomas.\textsuperscript{6,15,20,31} In this study, insular nonputaminal tumors were more likely to cause seizures than tumors involving the putamen. Furthermore, \textit{IDH1} mutation was more likely to occur in tumors that did not involve the putamen. Therefore, putaminal tumors may have a higher malignancy than nonputaminal tumors. In addition, previous studies have demonstrated that less malignant gliomas were associated with greater occurrences of tumor-related seizures.\textsuperscript{20,33,38} Therefore, the different seizure frequencies identified between the 2 cohorts in the current study may be attributable to the various biological features of gliomas.

The prognostic roles of the different classification systems of insular gliomas have rarely been investigated. A previous study suggested that Yaşargil Type 5A/B tumors with frontal extensions can predict good survival outcomes in all grades of insular gliomas,\textsuperscript{24} whereas another study failed to identify a correlation between Yaşargil type and patient morbidity.\textsuperscript{39} In the current study we proposed a new classification of insular gliomas based on the invasive capability of the tumor on MR images. Moreover, we examined the prognostic roles of both the putamen classification and Yaşargil’s classification using the same cohort of patients. We found that the putamen classification was associated with the survival outcomes of the patients, whereas no prognostic role was identified for Yaşargil’s classification. This lack of correlation may be explained by the fact that Yaşargil’s classification is based on an anatomical and developmental approach but does not consider tumor biological features. Berger-Sanai’s classification, an anatomy-based classification of insular glioma, can effectively predict extent of resection and perioperative morbidity.\textsuperscript{10,23} However, using the same data set from a single institute, we found no significant differences in survival

\begin{table}[h]
\begin{center}
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Characteristics & PFS & & & OS & & \\
\hline
\hline
Age (≥40 yrs) & 0.327 & 1.352 & 0.739–2.474 & 0.845 & 0.927 & 0.433–1.983 \\
Sex (male) & 0.238 & 1.420 & 0.794–2.541 & 0.658 & 1.166 & 0.592–2.297 \\
History of seizures (none) & 0.835 & 1.072 & 0.556–2.066 & 0.160 & 1.000 & 0.381–3.083 \\
Preop KPS score (<90) & 0.064 & 1.749 & 0.969–3.157 & 0.189 & 1.604 & 0.793–3.245 \\
Side (lt) & 0.251 & 1.388 & 0.793–2.429 & 0.059 & 1.875 & 0.976–3.602 \\
Lesion size (>mean) & 0.727 & 1.120 & 0.593–2.115 & 0.268 & 0.665 & 0.323–1.369 \\
Putamen involvement & \textbf{0.003} & 2.488 & 1.360–4.549 & \textbf{0.014} & 2.435 & 1.194–4.968 \\
Histopathology (astrocytoma) & 0.378 & 1.314 & 0.716–2.409 & 0.167 & 1.643 & 0.813–3.319 \\
Gross-total resection & 0.025 & 1.615 & 1.061–2.460 & 0.035 & 1.673 & 1.038–2.696 \\
\hline
\textit{IDH1} (wild type) & \textbf{0.001} & 2.603 & 1.474–4.596 & \textbf{0.026} & 2.121 & 1.092–4.120 \\
\hline
\end{tabular}
\end{center}
\caption{Multivariate analysis of survival outcomes*}
\end{table}

* Boldface type indicates significance.
outcomes among the 9 Berger-Sanai groups of insular gliomas. This negative statistical result could be attributed to the imbalance in patient numbers among the different groups.

Several previous studies have investigated the prognostic factors of insular gliomas.23–25 As in our study, extent of resection has been revealed to be a strong independent predictor of both PFS and OS.23–25 Moreover, IDH1 mutation has been found to be a good prognostic factor for gliomas.23,24,25 However, the prognostic value of IDH1 mutation was still unclear in insular LGGs. Only one recent study27 has shown that IDH1 mutation was associated with longer OS (univariate analysis) in patients with insular gliomas with resection ≥ 90%. Furthermore, in the current study we identified the putamen classification as another independent predictor of PFS and OS on multivariate Cox regression analysis. Specifically, patients with insular LGGs not involving the putamen had a significantly better prognosis than those with insular LGGs involving the putamen. In addition to the fact that putaminal tumors are less likely to be totally removed, these tumors may also have higher malignant biological features, and thus leading to a worse prognosis.

In previous studies, a younger age and favorable histological features (WHO Grade I and oligodendrogial tumors) were identified as independent predictors of survival in all-grade insular gliomas.24 In a study on nonenhancing insular gliomas,25 the histological type (WHO Grade II) and a small tumor volume (< 20 cm3) were revealed to be independent predictors of OS. In the present study, however, age at diagnosis was not a predictor of survival outcome. But the majority of patients were young at the first diagnosis (median age 38 years), which may be the reason for the lack of prognostic ability of age at diagnosis for insular LGGs.

Several limitations of this study should be considered. Putaminal involvement was qualitatively identified by experienced neuroradiologists, whereas the degree of tumor involvement was not quantitatively assessed. In addition, there were limited data on other molecular biomarkers, such as ATRX; thus, unfortunately, these data were not included in the multivariate model. The genomic profiles regarding various classifications of insular gliomas would be an interesting issue to investigate in the future.

Conclusions

In this study, a novel classification of insular gliomas based on the preoperative MRI manifestation was proposed. In a consecutively collected cohort, putamen involvement was shown to be an independent predictor of worse survival outcomes in patients with insular LGGs. Owing to its prognostic value, this newly proposed classification scheme may allow for the preoperative prediction of survival in patients with insular glioma.

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References


Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Jiang, Yongheng Wang, Yinyan Wang. Acquisition of data: Fan. Analysis and interpretation of data: Yongheng Wang, Yinyan Wang, Fan, Liu. Drafting the article: Jiang, Yongheng Wang, Yinyan Wang. Reviewed submitted version of manuscript: Jiang, Yongheng Wang, Yinyan Wang, Fan, Li, J Wang. Reviewed submitted version of manuscript: Jiang, Yongheng Wang, Yinyan Wang, Fan, Li. Approved the final version of the manuscript on behalf of all authors: Jiang. Statistical analysis: Yongheng Wang, Yinyan Wang, Fan, Li. Administrative/technical/material support: all authors. Study supervision: Jiang, Liu, J Wang.

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*Supplemental Figure and Tables.* https://thejns.org/doi/suppl/10.3171/2016.5.JNS1685.

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