Impact of gross total resection in patients with WHO grade III glioma harboring the IDH 1/2 mutation without the 1p/19q co-deletion

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Abstract The prognosis of patients with WHO grade III gliomas is highly dependent on their genomic status such as the isocitrate dehydrogenase (IDH) 1/2 mutation and 1p/19q co-deletion. However, difficulties have been associated with determining which tumors have certain genomic profiles by preoperative radiographic modalities, and the role of surgical resection in achieving better outcomes remains unclear. This retrospective study included 124 consecutive patients with newly diagnosed grade III gliomas. The genomic status of IDH1/2 and 1p/19q was analyzed in these patients. Tumors were then divided into 3 subgroups based on their genomic status; the IDH 1/2 mutation with the 1p/19q co-deletion (1p/19q co-del), the IDH 1/2 mutation without the 1p/19q co-deletion (non-1p/19q co-del), and the IDH 1/2 wild type (IDH wt). Survival times were compared between patients who underwent gross total resection and those who did not (GTR versus non-GTR). The relationships between genomic statuses and MR imaging characteristics such as ring-like or nodular enhancements by gadolinium, and very low intensity on T1-weighted images with blurry enhancements (T1VL) were also examined. Among all patients with grade III gliomas, GTR patients had longer median survival and progression-free times than those of non-GTR patients (undefined versus 87 months, \( p = 0.097 \), and 124 versus 34 months, \( p = 0.059 \), respectively). No significant differences were observed in survival between GTR and non-GTR patients in the 1p/19q co-del group (\( p = 0.14 \)), or between GTR and non-GTR patients in the IDH wt group (26 and 27 months, \( p = 0.29 \)). On the other hand, in non-1p/19q co-del group, survival was significantly longer in GTR patients than in non-GTR patients (undefined versus 77 months, \( p = 0.005 \)). Radiographically, T1VL was detected in most tumors in the non-1p/19q co-del group (78.2%), but only 6 (21.4%) and 17 (41.5%) tumors in the 1p/19q co-del and IDH wt groups, respectively. A correlation was not found between other genomic subgroups and MR imaging findings. Strict surgical removal is important to improve the prognosis of patients with grade III gliomas, especially for tumors with the IDH 1/2 mutation. The MR finding of T1VL can be used to select candidates for more radical resection.

Keywords Glioma · WHO grade III · IDH · 1p/19q · Surgery · Magnetic resonance imaging

Abbreviations

CT Computed tomography
FLAIR Fluid-attenuated inversion recovery
GTR Gross total resection
IDH Isocitrate dehydrogenase
MGMT O6-methylguanine-methyltransferase
MR Magnetic resonance
OS Overall survival
PFS Progression-free survival
WHO World Health Organization

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Introduction

Anaplastic gliomas, which are defined as grade III by the World Health Organization (WHO) criteria [1], are considered to be malignant because of the short survival of patients with these gliomas. Furthermore, the prognosis of these patients varies depending on the histological subtype. Recent genome-wide mutational analyses revealed that this clinical heterogeneity was related to the status of certain genomes such as O6-methylguanine-methyltransferase (MGMT), 1p/19q, or isocitrate dehydrogenase 1/2 (IDH 1/2), which have been identified as prognostic indicators for malignant gliomas [2–12]. Our group and other studies reported that a mutation in the IDH 1/2 gene, which encodes the oxidation-reduction enzyme catalyzing the oxidative decarboxylation of isocitrate to alpha-ketoglutarate, improved the survival of patients with grade III gliomas [12–14]. The 1p/19q co-deletion, which is the common genomic aberration in oligodendrogliarial lineage gliomas, is also strongly associated with a favorable prognosis [10, 15–18]. Such genome mutation analyses are only available postoperatively, and difficulties are still associated with identifying which tumors have a better genomic profile based on preoperative radiographical findings.

The extent of resection is also known as a strong prognostic factor for malignant gliomas. Despite the development of adjuvant therapy with intensive radiation and chemotherapy, the prognoses of patients with malignant gliomas are still poor if gross total removal GTR cannot be achieved. The resection rate for glioblastomas, which are categorized as WHO grade IV, has been directly correlated with prognosis [19], while surgically acquired motor deficits have been associated with a poor prognosis [20]. Therefore, the maximum extent of resection achievable with minimum surgical morbidity is the primary aim of malignant glioma surgery. Although evidence has been accumulating for the importance of GTR in glioblastomas, the relationship between the extent of resection and prognosis in patients with grade III gliomas has not yet been clarified [18].

The aim of the present study was to clarify the importance of surgical resection for grade III gliomas. We retrospectively reviewed the relationship between the genomic status and radiographical characteristics, and determined whether it was possible to confirm preoperatively which tumor needed to be more radically resected in order to achieve a better outcome.

Clinical materials and methods

Clinical materials

We retrospectively studied 124 consecutive patients with WHO grade III gliomas who were treated at Tohoku University Hospital between 1997 and 2013, some of whom had been reported previously [7, 21, 22]. All patients were over 18 years of age at the time of surgery. Histological diagnoses were based on the WHO classification [1]. Follow-up duration was 4 to 201 (median 79.4) months after surgery. Informed consent was obtained from each patient or guardian on admission prior to computed tomography (CT) or MR imaging with contrast medium and surgical resection/radiochemotherapy. This study was approved by the Tohoku University Institutional Review Board.

Molecular marker status

Genomic aberrations in MGMT, IDH1, IDH2, 1p, and 19q

MGMT promoter methylation was analyzed by methylation-specific polymerase chain reaction (PCR), as described previously [7, 9]. PCR products were separated on 4% agarose gel containing ethidium bromide and the bands were visualized with ultraviolet light.

Direct sequencing for the IDH1 and IDH2 genes was carried out using the QIAamp DNA Mini Kit (Qiagen Science, Germantown Maryland, USA), as described previously [7, 8, 23]. Briefly, exon 4 of the IDH1 and IDH2 genes was amplified by PCR, and the products were subsequently purified. All sequence reactions were carried out using the GenomeLab DTCS quick-start kit (Beckman Coulter, Fullerton, CA, USA), and performed in an automated DNA analyzer (CEQ 8000; Beckman Coulter) [8].

The chromosome arm 1p and 19q deletions were detected by a multiplex ligation-dependent probe assay (Salsa MLPA, P088, MRC Holland, Amsterdam, the Netherlands), as described in detail elsewhere [7, 18, 24, 25] Briefly, this technique consisted of denaturing, hybridization, ligation, amplification, and a fragment analysis. Each probe amplification product was divided by the average of the reference probes to compensate for differences in the efficiency of PCR. The data obtained were divided by the corresponding average probe fraction of the normal sample. Above 1.2 or below 0.8 was considered as a gain or loss, respectively. Below 0.4 was considered as a homozygous deletion [18, 24–26].

Based on their genomic statuses, patients with grade III gliomas were divided into 3 subgroups (Fig. 1); the IDH 1/2 mutation with the 1p/19q co-deletion (1p/19q co-del), the IDH 1/2 mutation without the 1p/19q co-deletion (non-1p/19q co-del), and the IDH 1/2 wild type (IDH wt) [27].

Neuroimaging

All patients underwent preoperative, postoperative, and subsequent follow-up MR imaging at our department. Postoperative MR imaging was performed within 72 h of surgery.
Results

Patient characteristics

This study included 124 patients, 76 males and 48 females aged between 21 and 77 years (median 44 years), with WHO grade III gliomas (Table 1). The histological diagnosis was anaplastic astrocytoma in 60 patients, anaplastic oligodendroglioma in 39 patients, anaplastic oligoastrocytoma in 18 patients, and anaplastic ganglioglioma in 7 patients. The IDH 1/2 gene mutation was detected in 83 patients while the 1p/19q co-deletion was detected in 28 patients. The median follow-up time was 79.4 months.

Relationship between the extent of surgical resection and survival in all cases

Among the 124 cases examined, OS was compared between the GTR and non-GTR groups (Fig. 2, left panel). The median survival time of the GTR group was undefined, while that of non-GTR group was 87 months (p = 0.097).

Table 1
Clinical characteristics of 124 patients with WHO grade III glioma

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Valuea</th>
</tr>
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<tbody>
<tr>
<td>No. of cases</td>
<td>124</td>
</tr>
<tr>
<td>Age (years), range (median)</td>
<td>21–77 (44)</td>
</tr>
<tr>
<td>M/F ratio (% of female)</td>
<td>76:48 (32.3)</td>
</tr>
<tr>
<td>Follow up duration (months), range (mean)</td>
<td>4–201 (79.4)</td>
</tr>
<tr>
<td>Gross total resection</td>
<td>56 (45.2)</td>
</tr>
<tr>
<td>IDH 1/2 mutation</td>
<td>83 (67.0)</td>
</tr>
<tr>
<td>1p19q codeletion</td>
<td>28 (22.6)</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>60 (48.4)</td>
</tr>
<tr>
<td>Anaplastic oligodendroglioma</td>
<td>39 (31.5)</td>
</tr>
<tr>
<td>Anaplastic oligoastrocytoma</td>
<td>18 (14.5)</td>
</tr>
<tr>
<td>Anaplastic ganglioglioma</td>
<td>7 (5.6)</td>
</tr>
</tbody>
</table>

aData are presented as no. (%) unless otherwise indicated

Statistical analysis

Estimates of overall survival (OS), and progression-free survival (PFS) were calculated with the Kaplan–Meier method, and the log-rank (Mantel-Cox) test was used to evaluate differences between the groups. The relationship between the genomic status and radiographical characteristics was estimated with the Student’s t test. Probability values ≤0.05 were considered significant. SPSS software (IBM Japan, Tokyo, Japan) and Prism software (GraphPad Software, Inc., La Jolla, CA) were used for statistical analyses.
but relatively less frequent in IDH wt group. Most patients received nimustine hydrochloride (ACNU)-based chemotherapy, and temozolomide was chosen for some cases. All patients except three received radiation therapy. There was no difference in postoperative treatment strategy between genomic subgroups.

Disease progression, which is defined as local recurrence, distant recurrence, or diffuse meningeal dissemination, was observed in 8 out of 28 (28.6%) and 19 out of 55 (34.5%) patients in the 1p/19q co-del and non-1p/19q co-del groups, respectively, and in 29 out of 41 (70.7%) patients in the IDH wt group (Table 3). Disease progression occurred 4–79 months (median 24.4) after initial surgery. Some patients with disease progression underwent second surgery. Among the patients in the 1p/19q co-del group, 2 underwent second surgery, and their histological diagnoses were the same as the original tumor. On the other hand, among the patients in the non-1p/19q co-del group, 11 underwent second surgery, with 4 (36.4%) exhibiting malignant transformation into glioblastomas. Among the patients in the IDH wt group, 10 underwent second surgery, with 3 (30.0%) exhibiting malignant transformation into glioblastoma.

**Genomic status and role of surgical resection**

OS was compared between GTR and non-GTR patients in each genomic subgroup. Among the patients in the 1p/19q co-del group, the median survival time of neither GTR nor non-GTR patients was undefined, and no significant difference was observed in survival between these patients \( p=0.14, \text{Fig. 3a} \). On the other hand, among the patients in the non-1p/19q co-del group, the median survival time of GTR patients was undefined, while that of non-GTR patients was 77 months. Therefore, patients who achieved GTR had significantly longer survival times \( p=0.005, \text{Fig. 3b} \). There was no significant difference between in the baseline characteristics between GTR and non-GTR patients in non-1p/19q co-del group (Table 2). Among the patients in the IDH wt group, the median survival times of GTR and non-GTR patients were 26 and 27 months, respectively, and these were not significantly different \( p=0.29, \text{Fig. 3c} \).

**Difference in patient characteristics, disease progression and histological alterations between subgroups**

The baseline characteristics and postoperative treatment were compared between genomic subgroups (Table 3). The methylation of the MGMT promotor was frequently detected in 1p/19q co-del and non-1p/19q co-del groups, indicating that patients who achieved GTR had better survival. PFS was compared between the GTR and non-GTR groups (Fig. 2, right panel). The median PFS of the GTR and non-GTR groups were 124 and 34 months, respectively \( p=0.059 \), indicating that patients who achieved GTR had longer PFS.

The relationship between MR imaging findings and the genomic status was examined (Fig. 4). In the 1p/19q co-del group, ring-like and nodular enhancements were observed in 13 (46.4%) and 9 (32.1%) out of 28 patients, respectively, T1VL was observed in 6 (21.4%) patients. In the non-1p/19q co-del group, ring-like and nodular enhancements were detected in 4 (7.3%) and 8 (14.5%) out of 55 patients, respectively. T1VL was detected in 43 (78.2%) indicating that patients who achieved GTR had better survival. PFS was compared between the GTR and non-GTR groups (Fig. 2, right panel). The median PFS of the GTR and non-GTR groups were 124 and 34 months, respectively \( p=0.059 \), indicating that patients who achieved GTR had longer PFS.

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**Relationship between radiographical parameters and genomic status**

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The genomic status is known to be an important indicator for the prognosis of patients with grade III gliomas. MGMT promotor methylation, the 1p/19q co-deletion, and IDH 1/2 mutation have been associated with better treatment outcomes, even though a uniformed treatment strategy was applied [2, 4–6, 10, 11]. Maximum resection has been considered the basic aim of glioma surgery and this concept has been applied for any type of malignant glioma without consideration of the genomic status. In the present study, we confirmed that GTR was a generally important prognostic factor of grade III gliomas. The contribution of GTR to treatment outcomes varied and depended on the genomic profile of each tumor. We divided grade III gliomas into 3 subgroups based on genomic statuses of IDH1/2 and 1p/19q. The benefits of GTR is the highest for the group with the IDH 1/2 mutation without the 1p/19q co-deletion.

As suggested previously, the IDH 1/2 mutation and 1p/19q co-deletion are well known favorable prognostic factors. In the IDH wt group, ring-like enhancements, nodular enhancements, and T1VL with blurry enhancements were detected in 13 (31.7 %), 11 (26.8 %), and 17 (41.5 %) out of 41 patients, respectively. T1VL correlated with non-1p/19q co-del tumors, whereas no significant relationship was observed between other genomic subgroups and any MR imaging findings. Representative cases are shown in Figs. 5, 6, and 7.

**Discussion**

The genomic status is known to be an important indicator for the prognosis of patients with grade III gliomas. MGMT promotor methylation, the 1p/19q co-deletion, and IDH 1/2 mutation have been associated with better treatment outcomes, even though a uniformed treatment strategy was applied [2, 4–6, 10, 11]. Maximum resection has been considered the basic aim of glioma surgery and this concept has been applied for any type of malignant glioma without consideration of the genomic status. In the present study, we confirmed that GTR was a generally important prognostic factor of grade III gliomas. The contribution of GTR to treatment outcomes varied and depended on the genomic profile of each tumor. We divided grade III gliomas into 3 subgroups based on genomic statuses of IDH1/2 and 1p/19q. The benefits of GTR is the highest for the group with the IDH 1/2 mutation without the 1p/19q co-deletion.

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radiation prolonged the survival of patients with 1p/19q co-deletion, whereas there was no additional effect for patients without the 1p/19q co-deletion [3, 15]. Even though GTR was not achieved, subsequent radiochemotherapy controlled the residual tumors with 1p/19q co-deletion to some extent.

On the other hand, the prognosis of the non-1p/19q co-del group was not satisfactory. Histologically, most tumors in this group were considered to be classical anaplastic astrocytomas, which are less sensitive to radiation and/or chemotherapy. Furthermore, malignant factors for high grade gliomas [8, 10, 13, 15–17]. In our series, patients with tumors with the IDH 1/2 mutation and 1p/19q co-deletion had better outcomes. Interestingly, the survival of patients in the group without GTR was not inferior to that with GTR (Fig. 3a). One possible explanation for this is the sensitivity of radiation and/or chemotherapy. Carincross et al. reported that intensive chemotherapy with radiation prolonged the survival of patients with 1p/19q co-deleted gliomas, whereas there was no additional effect for patients without the 1p/19q co-deletion [3, 15]. Even though GTR was not achieved, subsequent radiochemotherapy controlled the residual tumors with 1p/19q co-deletion to some extent.

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<table>
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<th>Table 3</th>
<th>Postoperative treatment and malignant transformation in each subgroup</th>
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<tr>
<td>Characteristics</td>
<td>IDH 1/2 mutant</td>
</tr>
<tr>
<td>No. of cases</td>
<td>28</td>
</tr>
<tr>
<td>Age (years), range (median)</td>
<td>38–70 (50)</td>
</tr>
<tr>
<td>Tumor volume (cm³), mean ± SE</td>
<td>66.9 ± 13.2</td>
</tr>
<tr>
<td>GTR: Non-GTR</td>
<td>11:17</td>
</tr>
<tr>
<td>MGMT methylation</td>
<td>23 (82.1)</td>
</tr>
<tr>
<td>Radiation</td>
<td>26 (89.7)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>ACNU</td>
<td>22 (78.6)</td>
</tr>
<tr>
<td>TMZ</td>
<td>2 (7.1)</td>
</tr>
<tr>
<td>Others</td>
<td>0</td>
</tr>
<tr>
<td>None</td>
<td>4 (14.3)</td>
</tr>
<tr>
<td>Disease progression</td>
<td>8 (28.6)</td>
</tr>
<tr>
<td>Second surgery</td>
<td>2</td>
</tr>
<tr>
<td>Malignant transformation</td>
<td>0</td>
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</table>

GTR gross total resection, SE standard error, TMZ temozolomide

Fig. 4 Relationship between magnetic resonance imaging findings and the genomic status of the tumor. T1VL was demonstrated in 43 out of 55 gliomas with the IDH 1/2 mutation and non-1p/19q co-deletion, 6 out of 28 gliomas with the IDH 1/2 mutation and 1p/19q co-deletion, and 17 out of 41 gliomas with the IDH 1/2 wild type
In literatures, several authors mentioned the extent of resection, molecular subclassification and outcome. Keles et al. reported that the residual enhanced lesion after initial surgery was the most significant prognostic factor in patients with anaplastic astrocytoma [32]. Although they showed the importance of gross total resection, molecular status was not mentioned. Beiko et al. reported that complete resection was beneficial for IDH mutant tumors [33]. They investigated 335 patients, which was larger number,

Fig. 6  A 27-year-old woman with symptomatic epilepsy was referred to our department. Head MR imaging revealed a mass lesion on the left temporal lobe with very low intensity on T1-weighted images with blurry enhancements (left). The patient underwent surgery and post-operative MR imaging showed no residual lesions (middle). The histological diagnosis was anaplastic astrocytoma with the IDH 1/2 mutation and without the 1p/19q co-deletion. MR imaging, taken 29 months after surgery, showed a large and rapidly growing enhanced lesion along with the resection cavity (right). The patient underwent second surgery, and the histological diagnosis was glioblastoma.

Fig. 7  A 34-year-old man with symptomatic epilepsy was referred to our department. Head MR imaging revealed a nodular enhanced mass lesion on the left medial temporal lobe (left). The patient underwent surgery and post-operative MR imaging showed no residual lesions (middle). The histological diagnosis was anaplastic astrocytoma with wild type IDH 1/2. MR imaging, taken 9 months after surgery, showed a small enhanced lesion along with the resection cavity (right). The patient underwent second surgery, and the histological diagnosis was glioblastoma.

transformation into glioblastoma has been reported for the tumors with this genomic status (secondary glioblastoma) [31]. These findings may explain the poor prognosis of patients in the non-1p/19q co-del group, and, similar to glioblastomas, greater efforts are needed for more aggressive resection in order to prolong survival [19]. In our series, the survival of patients who achieve GTR was significantly longer than those without GTR (p = 0.005, Fig. 3).

In literatures, several authors mentioned the extent of resection, molecular subclassification and outcome. Keles et al. reported that the residual enhanced lesion after initial surgery was the most significant prognostic factor in patients with anaplastic astrocytoma [32]. Although they showed the importance of gross total resection, molecular status was not mentioned. Beiko et al. reported that complete resection was beneficial for IDH mutant tumors [33]. They investigated 335 patients, which was larger number,
but 207 glioblastomas (WHO grade IV) was also included, and 1p/19q codeletion was not mentioned. Compared to these reports, our results demonstrated that the association between molecular status and resection outcome is quite complicated, and strict resection is most beneficial for grade III gliomas with IDH mutation without 1p/19q co-deletion. Another report showed that the resectability was independent of molecular status, such as such as IDH mutation and 1p/19q co-deletion [34]. In our series, there was no difference in resection rate between 3 subgroups, which is consistent with these reports.

The present study also revealed a strong correlation between the non-1p/19q co-del tumor subtype and MR findings of T1VL. On the other hand, we did not find significant relationships between any MR findings and other tumor subtypes (Fig. 4). These results are partially consistent with previous findings. A correlation was previously reported between MR findings and genomic profiles such as MGMT and epidermal growth factor receptor amplification, in oligodendrogliomas and glioblastomas [35–38]; however, the relationship between MR findings of the IDH mutation status remains controversial. Qi et al. reported that contrast enhancement in IDH-mutated gliomas [39], and Reyes-Botero et al. demonstrated no specific imaging pattern was identifiable for IDH-mutated anaplastic oligodendrogliomas [28]. Lai et al. reported that IDH mutant glioblastomas were associated with frontal location and less contrast enhancement [40]. They stated this radiographical pattern was consistent with low grade gliomas, so that this finding can support the concept that IDH mutant glioblastoma arise from neural precursor populations. They also showed that IDH mutant gliomas have less vascular abnormalities. Although there are possibilities that other genomic changes can be associated with contrast enhancement pattern, it is useful in a clinical setting to identify tumors that need to be radically resected, preoperatively. Even though the tumor on the eloquent area cannot be resected, this information might be significant for surgeons to obtain maximum resection. More precise imaging modalities such as MR spectroscopy are recommended for detecting these genomic statuses [41].

The present study had some limitations. Our study is retrospective study and the number of patients was limited, which can potentially introduce biases. In this study, GTR was not of less significance in terms of the outcome for the non-1p/19q co-del and IDH wt groups. This can be to relatively short follow up and small sample size. More patients and longer follow up duration are required for a better understanding of prognostic factors and radiographical findings. Furthermore, this was a single-institution study. Surgical outcomes are highly dependent on the operator’s skill; therefore, our results cannot be directly compared with the findings of other studies. We also included the patients with anaplastic oligoastrocytoma, which is now controversial as histological diagnosis [42, 43]. This is retrospective study, and there must be inconsistency between molecular and histological diagnosis. Prospective analysis should be conducted. In addition, there are some other molecular markers which we did not investigate, such as TP53 or ATRX (alpha thalassemia/mental retardation syndrome X-linked). We used IDH 1/2 and 1p19q statuses to classify grade III gliomas, as reported previously [44]. Exhaustive analysis should be conducted to assess this matter. However, we considered it important to demonstrate that tumors with the IDH1/2 mutation and without the 1p/19q co-deletion were identifiable with MR findings, and needed to be more aggressively resected.

Conclusion

In the present study, we showed the importance of surgical resection for grade III gliomas, and demonstrated that the prognoses of patients with tumors with the IDH1/2 mutation and without the 1p/19q co-deletion may be improved when GTR is achieved. Preoperative MR findings of very low intensity on T1-weighted images with blurry enhancements may be the distinctive characteristics of gliomas with the IDH1/2 mutation and without the 1p/19q co-deletion. The strict resection of tumors in this patient population may lead to better treatment outcomes.

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