Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms

SONGTAO QI1*, LEI YU1*, HEZHEN LI1, YANGHUI OU1, XIAOYU QIU1, YANQING DING2, HUIXIA HAN2 and XUELIN ZHANG3

Departments of 1Neurosurgery, 2Pathology and 3Radiology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong 510515, P.R. China

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Abstract. The molecular subsets of glioma behave in biologically distinct ways. The present study detected isocitrate dehydrogenase (IDH) 1 and IDH2 mutations in glioma to analyze whether IDH-mutated gliomas are situated in certain preferential areas and to investigate their correlation with magnetic resonance imaging (MRI) characteristics. A series of 193 patients with astrocytic neoplasms (111 diffuse and 82 anaplastic astrocytomas), grouped according to prelabeled anatomical structures and the risk of surgery, were retrospectively reviewed for IDH1 and IDH2 mutations to compare the tumor location and MRI features. A total of 111 IDH1 mutations at codon 132 (57.5%) and six IDH2 mutations at codon 172 (3.1%) were detected. The IDH1/2 mutations were found to predict longer survival, independent of the histological type in this series of patients. The IDH-mutated gliomas were predominantly located in a single lobe, such as the frontal lobe, temporal lobe or cerebellum and rarely in the diencephalon or brain stem. Furthermore, according to the risk of surgery, the IDH-mutated tumors were rarely located in the high-risk regions of the brain, where surgery exhibits a high mortality rate intraoperatively and postoperatively. In addition, gliomas with IDH mutations were significantly more likely to exhibit a unilateral pattern of growth, sharp tumor margins, homogeneous signal intensity and less contrast enhancement on MRI. The results of the current study suggested that the prolonged survival of patients with IDH-mutated gliomas is primarily due to a less aggressive biological behavior according to tumor site and MRI features.

Introduction

Gliomas are the most common type of tumor of the central nervous system in adults, with the glioma subtype, glioblastoma multiforme, the most common (1). A previous genome-wide mutational analysis of glioblastomas identified novel mutations in the isocitrate dehydrogenase (IDH) 1 gene (2). Further studies have demonstrated that IDH1 mutations are present in 50-90% of cases of grade II and III astrocytoma and oligodendroglioma, but rarely present in primary glioblastoma or pilocytic astrocytoma (3-11). In addition to IDH1 mutations, mutations in the homologous gene, IDH2, have also been identified in gliomas, but are much less common than the IDH1 mutations (12,13).

Various retrospective and prospective studies have demonstrated that the IDH mutation is associated with longer survival in glioma patients (12-15). However, none of these studies have analyzed the correlation between IDH status and tumor location/magnetic resonance imaging (MRI) characteristics. Notably, different intracranial locations, such as functional or non-functional lobes, as well as the cortex or deep brain, are likely to cause variable difficulty levels for surgery, and thus, correspondingly influence the prognosis of patients. Furthermore, different presurgical MRI features, including well-defined or blurred interfaces, homogeneous or heterogeneous signal intensity and contrast enhancement level, are also likely to result in different extents of resection and residual tumor and therefore, different prognoses.

Since IDH mutation, tumor location and MRI features correlate with patient prognosis in glioma, the aim of the present study was to clarify the tumor location and MRI features of IDH-mutated gliomas to determine whether the prolonged survival of IDH-mutated patients is associated with tumor location and presurgical MRI features. Therefore, the radiological and genetic features of 193 patients affected by astrocytic neoplasms, with specific associations with IDH gene status were analyzed to address the aforementioned issues.

*Contributed equally

Key words: isocitrate dehydrogenase, astrocytoma, tumor location, magnetic resonance imaging, prognosis
Materials and methods

Tumor samples. Patients were selected from a database of glioma patients treated at the Nanfang Hospital (Guangzhou, China) between January 2003 and December 2007. The eligibility criteria were as follows: Unequivocal pathological diagnosis according to the 2007 World Health Organization (WHO) criteria (16); availability of genetic analysis for IDH1/2; MRI scan at the time of the diagnosis or during the perioperative period; and ≥18 years old at the time of surgery. Following approval from the institutional review board, 193 evaluable patients with astrocytic neoplasms, consisting of 111 diffuse astrocytomas (DA) and 82 anaplastic astrocytomas (AA), were selected. The archival surgical specimens were enrolled after all patients had provided written informed consent allowing the molecular analysis of their tumor specimens. The pathology slides were reviewed by two neuropathologists and all tumor samples were confirmed by microscopic examination in which ≥70% of the visible cells in the section were tumor cells.

Radiological assessment. All patients underwent MRI scanning prior to and following surgery (within 72 h) to evaluate the extent of surgery. All the MRI scans were independently reviewed by two neuroradiologists and a neurosurgeon blinded to the genetic alterations in the tumors. The tumor location and the following MRI features were evaluated qualitatively: Unilateral versus bilateral pattern of growth (tumors that traversed the corpus callosum to involve the opposite cerebral hemisphere were determined to be bilateral); sharp versus indistinct tumor margins; homogeneous versus heterogeneous signal intensity; absent or slight versus significant contrast enhancement; absent or moderate versus severe mass effect; and absent or moderate versus severe edema.

To define the tumor location, the following grouping methods were considered. Tumor location defined using the following prelabeled anatomical structures in the brain: i) Frontal, temporal, parietal, occipital lobes and cerebellum; ii) insula, diencephalon, basal ganglia; and iii) brain stem. Tumor location divided into the following three groups according to the risk of surgery: Group I, high-risk regions (such as the hypothalamus, midbrain and medulla oblongata); group II, functional regions (for example the primary sensorimotor area, supplementary motor area, internal capsule and basal ganglia); and group III, non-functional regions (remote from high-risk regions and functional regions) at the time of diagnosis (Figs. 1-3). Regardless of the grouping methods, the tumor location was typically determined by joint analysis of sagittal, coronal and axial MRI sequences. In addition, the site of origin and location of the epicenter of the tumor were considered simultaneously to determine the tumor location.

IDH1/2 mutation analysis. Genomic DNA was extracted from the formalin-fixed, paraffin-embedded tissues using the QIAamp DNA mini kit (Qiagen, Hilden, Germany) according to the manufacturer’s instructions. IDH1 and IDH2 alterations characterized by mutual hotspots at codons R132 and R172, respectively, were assessed by high resolution melting (HRM) analysis (17) and direct sequencing, which were performed using the ABI PRISM 3730xl DNA analyzer (Applied Biosystems, Carlsbad, CA, USA). The polymerase chain reaction (PCR) products generated after HRM were sequenced directly following purification with the QIAquick PCR purification kit (Qiagen, Valencia, CA, USA). The PCR primers for mutations were designed using Primer Express software version 3.0 (Applied Biosystems). The primers sequences used were as follows: Forward, 5’-CGGTCTTTCAGAGAAGCATT-3’ and reverse, 5’-GCAAATCACATTATGGCCAAC-3’ for IDH1; and forward, 5’-CCAAGCCCATCACCATTG-3’ and reverse, 5’-ACTGGAGCTCCTCGCTTACG-3’ for IDH2. The PCR and HRM analyses were performed in a single run using the LightCycler 480 instrument (Roche Diagnostics GmbH, Penzberg, Germany) in a reaction mixture to discriminate between the wild-type and mutant DNA. Samples exhibiting conflicting HRM and direct sequencing results were retested and only the HRM-positive samples confirmed by direct sequencing were considered mutated.

Statistical analysis. Statistical analyses were conducted using SPSS version 13.0 (SPSS, Inc., Chicago, IL, USA). The χ2 test (or Fisher’s exact test when one subgroup was n<5) was used to determine the significance of associations. The Bonferroni test was used for multiple comparisons and the independent samples t-test was used to compare data acquired in each group for patients age. Progression-free survival (PFS) and overall survival (OS) were used to analyze the prognostic impact of IDH1/2 mutations. PFS was calculated from the initial surgery until the first unequivocal clinical or radiological sign of progressive disease, or the last follow-up (for censored cases) and OS was defined as the time between the initial surgery and mortality, or the last follow-up (for censored cases). The survival distributions were estimated using the Kaplan-Meier method and compared among the patient subsets using log-rank tests. All statistical tests were two-sided and P<0.05 was considered to indicate a statistically significant difference. Patients who succumbed to the disease within two months for DA and one month for AA following surgery were excluded from the analysis to avoid the inclusion of cases in which mortality may have been attributable to surgical complications.

Results

IDH1 and IDH2 mutations. A total of 193 astrocytic neoplasms, which fulfilled the inclusion criteria, were retrospectively analyzed. IDH1 and IDH2 mutations were identified in 57.5% (111/193) and 3.1% (6/193) of the patients, respectively. All IDH1 mutations were located at the amino acid residue 132, of which 102 were R132H (G395A Arg132His), six were R132C (C394T Arg132Cys) and three were R132S (C394A Arg132Ser) mutations, whereas all IDH2 mutations were observed at the amino acid residue 132, of which four were R172K (G515A Arg172Lys) and two were R172M (G515T Arg172Met) mutations. As previously reported (18,19), these two mutations are mutually exclusive as observed in 100% of cases in this series, suggesting that they are involved in similar tumorigenesis pathways. Therefore, in the current statistical analysis the IDH1 and IDH2 mutations were grouped together. The main clinical characteristics of the patients are summarized in Table I.
IDH1/2 mutations predict longer survival. The mean follow-up of the patients was 63.3 months (range, 15-101 months) and as indicated in Table I, a significant difference was indicated between patients with and without the IDH1/2 mutations and PFS (P<0.001) and OS (P<0.001), independent of WHO grade. The prognostic impact of the IDH1/2 mutations in
Table I. Main clinical characteristics.

| Variables                        | Total population | IDH1/2 mutations | IDH wild-type | P-value |
|----------------------------------|------------------|------------------|---------------|---------|
| n, (%)                           | 193 (100)        | 117 (60.6)       | 76 (39.4)     |         |
| Age, years                       |                  |                  |               | <0.001  |
| Median                           | 36.5             | 32.7             | 42.5          |         |
| Range                            | 18-72            | 19-67            | 18-72         |         |
| Gender, n (%)                    |                  |                  |               |         |
| Male                             | 109 (100)        | 65 (59.6)        | 44 (40.4)     |         |
| Female                           | 84 (100)         | 52 (61.9)        | 32 (38.1)     |         |
| KPS at diagnosis, n (%)          |                  |                  |               | 0.289   |
| ≥80                              | 119 (100)        | 76 (63.9)        | 43 (36.1)     |         |
| <80                              | 74 (100)         | 41 (55.4)        | 33 (44.6)     |         |
| Extent of surgery, n (%)         |                  |                  |               | 0.002   |
| Biopsy/PR                        | 89 (100)         | 43 (48.3)        | 46 (51.7)     |         |
| STR/GTR                          | 104 (100)        | 74 (71.2)        | 30 (28.8)     |         |
| PFS, months                      |                  |                  |               | <0.001  |
| Median                           | 45.8             | 56.7             | 34.4          |         |
| 95% CI                           | 42.0-49.6        | 51.1-62.3        | 29.1-39.7     |         |
| OS, months                       |                  |                  |               | <0.001  |
| Median                           | 71.3             | 84.3             | 57.3          |         |
| 95% CI                           | 66.1-76.5        | 79.0-89.6        | 46.2-68.4     |         |

AA, anaplastic astrocytoma; DA, diffuse astrocytoma; GTR, gross total resection; IDH1/2, isocitrate dehydrogenase 1/2 mutation; KPS, Karnofsky performance status; OS, overall survival; PR, partial resection; PFS, progression-free survival; STR, subtotal resection; WHO, World Health Organization; CI, confidence interval.

Figure 3. Patient with histological World Health Organization grade III anaplastic astrocytoma and no isocitrate dehydrogenase 1/2 mutation. Magnetic resonance imaging (A) T2-weighted, (B) T1-weighted and (C) postcontrast T1-weighted axial as well as post-contrast T1-weighted (D) sagittal and (E and F) coronal images demonstrated an ill-defined mass severely invading the medulla oblongata (high-risk region). The lesion showed heterogeneous T2 hyperintense and T1 iso-hyperintense signals with apparent enhancement following the contrast administration and a significant mass effect was observed without edema.
Table II. Analyzing the frequency of IDH1/2 mutations and tumor location according to anatomical structures.

| Histology | F, n | T, n | P or O, n | Multilobes, n | I or BG, n | D or BS, n | CB, n |
|-----------|------|------|-----------|---------------|-----------|-----------|-------|
| DA        |      |      |           |               |           |           |       |
| n         | 45   | 9    | 9         | 11            | 14        | 12        | 11    |
| IDH mutation | 38   | 7    | 8         | 3             | 6         | 1         | 9     |
| IDH wild-type | 7    | 2    | 1         | 8             | 8         | 11        | 2     |
| AA        |      |      |           |               |           |           |       |
| n         | 21   | 16   | 8         | 17            | 4         | 14        | 2     |
| IDH mutation | 15   | 13   | 4         | 5             | 3         | 4         | 1     |
| IDH wild-type | 6    | 3    | 4         | 12            | 1         | 10        | 1     |
| Overall   |      |      |           |               |           |           |       |
| n         | 66   | 25   | 17        | 28            | 18        | 26        | 13    |
| IDH mutation | 53   | 20   | 12        | 8             | 9         | 5         | 10    |
| IDH wild-type | 13   | 5    | 5         | 20            | 9         | 21        | 3     |

AA, anaplastic astrocytoma; BG, basal ganglia; BS, brain stem; CB, cerebellum; D, diencephalon; DA, diffuse astrocytoma; F, frontal lobe; IDH, isocitrate dehydrogenase; I, insular lobe; multilobes, combined lobes; O, occipital lobe; P, parietal lobe; T, temporal lobe.

Discussion

The tumor location and MRI features of gliomas are important indicators of prognosis and the tumor location determines the resectability of the glioma; tumors located in the critical areas of the brain are typically non-resectable whereas those located in the non-functional regions may undergo en bloc extended resection to prolong survival. MRI findings which are suggestive of high-grade gliomas, including a bilateral pattern of growth, undefined margins, mixed signal intensity and significant enhancement reflect increased ‘invasiveness’ and high malignancy of the glioma, which often indicate unfavorable outcomes. Notably, increasing age has classically been associated with a poor prognosis in gliomas and patients with IDH wild-type tumors are significantly older than those with IDH-mutated tumors, which is consistent with the results of the present study (Table I) (2,3,5,7). However, few studies have analyzed the correlation between IDH status and tumor location/MRI characteristics.

Recently, Metellus et al (20) reported that IDH wild-type WHO grade II gliomas are preferentially located in the fronto-temporo-insular region and exhibit a greater volume and therefore, require a reduced extent of surgery and demonstrate an infiltrative pattern on MRI. This is the only study to identify a statistically significant correlation between IDH status and specific brain subregions of tumor locations. By contrast, patients with oligodendrogial tumors were excluded in the current study as astrocytoma and oligodendroglioma exhibit different biological behaviors and clinical features (21-23). In addition, the correlation between IDH status and tumor location was analyzed in the present study based on a larger sample size and more comprehensive grouping methods, determined not only by prelabeled anatomical structures but also by the risk of surgery. The IDH-mutated gliomas were rarely found to locate in the high-risk regions of brain, such as the diencephalon or brain stem, where surgical resection is limited and exhibits a high mortality rate intraoperatively and postoperatively. The
**Table III. Analyzing the frequency of the IDH1/2 mutations and tumor location according to the risk of surgery.**

| Variables                | Group I vs. II | Group I vs. III | Group II vs. III |
|--------------------------|----------------|----------------|-----------------|
| Overall, n (%)           | 37 vs. 63      | 37 vs. 93      | 63 vs. 93       |
| IDH mutation             | 11 (29.7) vs. 39 (61.9) | 11 (29.7) vs. 67 (72.0) | 39 (61.9) vs. 67 (72.0) |
| IDH wild-type            | 26 (70.3) vs. 24 (38.1) | 26 (70.3) vs. 26 (80.0) | 24 (38.1) vs. 26 (80.0) |
| $\chi^2$ test            | 9.653          | 19.746         | 1.773           |
| P-value                  | 0.003          | <0.001         | 0.222           |

*Bonferroni test was performed for multiple comparisons and Bonferroni-corrected P<0.05/3 was considered to indicate a statistically significant difference. Groups I, high-risk; II, function regions; and III, non-functional regions. IDH, isocitrate dehydrogenase.

**Table IV. Analyzing the frequency of IDH1/2 mutations and different MRI features of gliomas.**

| MRI features          | All$, n (%) | P-value | DA$, n (%) | P-value | AA$, n (%) | P-value |
|-----------------------|-------------|---------|------------|---------|------------|---------|
| Pattern of growth     |             |         |            |         |            |         |
| Unilateral            | 116/178 (65.2) | <0.001  | 71/104 (68.3) | 0.007   | 45/74 (60.8) | 0.001   |
| Bilateral             | 1/15 (6.7)   |         | 1/7 (14.3)  |         | 0/8 (0.0)   |         |
| Tumor margins         |             |         |            |         |            |         |
| Sharp                 | 66/85 (77.6) | <0.001  | 44/55 (80.0) | 0.001   | 22/30 (73.3) | 0.012   |
| Indistinct            | 51/108 (47.2) |         | 28/56 (50.0) |         | 23/52 (44.2) |         |
| Tumor signal intensity|             |         |            |         |            | <0.001  |
| Homogeneous           | 70/89 (78.7) | <0.001  | 45/58 (77.6) | 0.003   | 25/31 (80.6) | <0.001  |
| Heterogeneous         | 47/104 (45.2) |         | 27/53 (50.9) |         | 20/51 (39.2) |         |
| Contrast enhancement  |             | <0.001  |            | 0.001   |            | 0.003   |
| Absent or slight      | 74/97 (76.3) |         | 47/60 (78.3) |         | 27/37 (73.0) |         |
| Significant           | 43/96 (44.8) |         | 25/51 (49.0) |         | 18/45 (40.0) |         |
| Mass effect           |             | 0.654   |            | 0.320   |            | 0.216   |
| Absent or moderate    | 47/75 (62.7) |         | 38/54 (70.4) |         | 9/21 (42.9) |         |
| Severe                | 70/118 (59.3) |         | 34/57 (59.6) |         | 36/61 (59.0) |         |
| Edema                 |             | 0.181   |            | 0.533   |            | 0.375   |
| Absent or moderate    | 71/109 (65.1) |         | 49/73 (67.1) |         | 22/36 (61.1) |         |
| Severe                | 46/84 (54.8) |         | 23/38 (60.5) |         | 23/46 (50.0) |         |

*Number of mutated samples/total number of samples of given type grouped by the different MRI features of gliomas. AA, anaplastic astrocytoma; DA, diffuse astrocytoma; MRI, magnetic resonance imaging; IDH, isocitrate dehydrogenase.

**IDH**-mutated gliomas were instead preferentially found to locate in the functional or non-functional regions, particularly the frontal and temporal lobes, where tumors can be removed easily. These results were supported by the observation that the extent of surgery (gross total resection and subtotal resection) was significantly higher in IDH-mutated gliomas compared with IDH wild-type gliomas (P=0.002; Table I).

This correlation between genotype and tumor site has also been reported in oligodendrogliomas and glioblastoma. Furthermore, in a pioneering study by Zlatescu et al (24), the anaplastic oligodendrogliomas located in the frontal, parietal and occipital lobes were significantly more likely to harbor the 1p19q codeletion than tumors arising in the temporal lobe, insula and diencephalon. More recent studies have identified a significant correlation between the 1p19q codeletion and tumor location in oligodendrogliomas or oligoastrocytomas (25-29). However, conflicting results have been reported regarding the correlation between O6-methylguanine DNA methyltransferase (MGMT) promoter methylation status and tumor location in glioblastoma. Eoli et al (30) also demonstrated that tumors with MGMT promoter methylation were more frequently located in the parietal and occipital lobes, whereas tumors without were frequently located in the temporal lobes, however, other studies have not identified such a correlation (31). In addition, astrocytomas have not been found to exhibit different frequencies of the 1p19q codeletion or tumor protein p53 mutations with respect to tumor location (25,26). Significant associations have also been reported between MRI characteristics and genotype in oligodendrogliomas, oligoastrocytomas or glioblastomas (20,29,31-37), however,
**IDH mutation status** was not addressed in these studies, with the exception of that by Metellus et al. Consistent with the results reported by Metellus et al (20), the present study also revealed that IDH-mutated gliomas are significantly more likely to exhibit sharp tumor margins. Furthermore, it was observed that IDH-mutated tumors tend to exhibit a higher incidence of unilateral pattern of growth, homogeneous signal intensity and less contrast enhancement. Therefore, the IDH-mutated tumors exhibit less invasiveness when compared with IDH wild-type tumors in MRI.

It is evident that the presence of IDH mutations is of major prognostic significance for patient outcome in gliomas and the current study found a marked correlation between the IDH mutations and OS (independent of WHO grade) in this series of patients. However, at present, the underlying mechanism of IDH mutations in tumorigenesis and prognostic significance remains unclear. A prospective randomized European Organization for Research and Treatment of Cancer study 26951 reported by van den Bent et al (38), revealed no indication that the presence of the IDH1 mutation predicts the outcome to adjuvant procarbazine, 1-(2-chloroethyl)-3-cyclohexyl-nitrosourea, and vincristine chemotherapy. In an additional retrospective report on temozolomide chemotherapy in low grade astrocytoma, no correlation was identified between outcome and the IDH mutations (39). These results suggested that the improved survival observed in IDH1-mutated tumors is primarily due to a less aggressive biological behavior and not due to an improved outcome for chemotherapy treatment (38).

In conclusion, the current study investigated the correlation between IDH status and tumor location, as well as MRI characteristics in astrocytic neoplasms and revealed that the prolonged survival of patients with IDH1-mutated tumors is primarily due to a less aggressive biological behavior from the perspective of tumor site and MRI features.

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