**Isocitrate Dehydrogenase (IDH)1/2 Mutations as Prognostic Markers in Patients With Glioblastomas**

**Jun-Rui Chen, MD, Yu Yao, MD, Hong-Zhi Xu, MD, and Zhi-Yong Qin, MD, PhD**

**Abstract:** The purpose of this study was to perform a meta-analysis examining the association of isocitrate dehydrogenase (IDH)1/2 mutations with overall survival (OS) and progression-free survival (PFS) in patients with glioblastomas.

Medline, Cochrane, EMBASE, and Google Scholar were searched from inception to January 28, 2015, using combinations of the following keywords: IDH mutation, brain tumor, glioma, glioblastoma, oligodendroglioma, prognosis. Randomized controlled trials, and prospective and retrospective studies of patients with glioblastomas that provided IDH mutation and survival data were included. OS and PFS were used to evaluate the association of IDH1 and IDH1/2 mutations and prognosis. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for OS and PFS were calculated and compared between patients with and without mutations.

Of 165 studies that were identified, 136 nonrelevant studies were excluded. Twenty-nine full-text articles were assessed, and of these, 5 were excluded as they did not provide a quantitative outcome. Therefore, 24 studies were included in the qualitative synthesis. The pooled HR of 0.358 (95% CI 0.264–0.487, P < 0.001) indicated that IDH mutations were associated with better OS. Similarly, the pooled HR of 0.322 (95% CI 0.264–0.455, P < 0.001) indicated that IDH mutations were associated with better PFS. When patients were stratified by surgery versus surgery or IDH1 versus IDH1/2 mutations, the results also indicated that the presence of IDH mutations was associated with better OS and PFS.

The IDH mutations are associated with improved survival in patients with glioblastomas.

**INTRODUCTION**

Glioblastomas (glioblastoma multiforme [GBM]) are the most common and aggressive malignant brain tumor, with a median survival from diagnosis of approximately 12 to 14 months. The majority of glioblastomas (~90%) occur without evidence of a less malignant precursor lesion (primary glioblastomas) in older patients, whereas secondary glioblastomas progress from low-grade diffuse astrocytoma or anaplastic astrocytoma, and occur in younger patients. Secondary glioblastomas have a significantly better prognosis than primary glioblastoma.

Approximately 70% to 80% of secondary glioblastomas have somatic mutation in the isocitrate dehydrogenase 1 (IDH1) gene, which are absent in primary glioblastoma. Wild-type IDH1 protein is found in the cytoplasm, peroxisomes, and endoplasmic reticulum, and catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate. Mutations in IDH1 associated with glioblastomas map to the highly conserved residue R132 in the enzyme active site, and usually result in an Arg to His substitution, although other substitutions can also occur. The IDH1 R132 mutation occurs in 55% to 80% of grade II and III oligodendrogliomas and astrocytomas, but is rare in primary glioblastomas. To a lesser extent, glial tumors have somatic mutations in the corresponding codon (codon R172) of the IDH2 gene. The IDH2 protein has a similar function to IDH1, but is found in the mitochondria. Both the IDH1-R132 and IDH2-R172 mutations are thought to result in an accumulation of the oncometabolite 2-hydroxyglutarate instead of α-ketoglutarate.

It is unclear how a tumor’s biology is affected by IDH1/2 mutations. IDH1/2 mutations may result in genome-wide epigenetic changes in human gliomas. Another hypothesis is that the mutations reduce the capacity of cells to produce NADPH, and consequently lowers the ability of the cell to scavenge oxygen species, making the tumor cells more susceptible to irradiation and chemotherapy. This increased sensitivity to treatments may result in increased patient survival.

A number of studies have found that IDH1-R132 and IDH2-R172 mutations are linked to the genomic profile of the tumor, and are important prognostic markers in grade II to IV gliomas. However, other studies have not found an association of IDH1/2 mutations with prognosis in low-grade tumors. Therefore, the prognostic value of these genetic markers for survival is not clear.

The purpose of the current study was to perform a meta-analysis to examine the association of IDH1/2 mutations with overall survival (OS) and progression-free survival (PFS) in patients with glioblastomas.

**METHODS**

**Literature Search Strategy**

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines. Medline, Cochrane, EMBASE, and Google Scholar were searched from inception to January 28, 2015, using combinations of the following keywords: IDH mutation, brain tumor, glioma,
glioblastoma, oligodendroglioma, prognosis. Reference lists of relevant studies were hand-searched. Meta-analyses do not involve humans and do not require Institutional Review Board approval.23

Study Selection and Data Extraction

Inclusion criteria were as follows: randomized controlled trials (RCTs) and prospective and retrospective studies; patients with a malignant brain tumor (glioma, glioblastoma, anaplastic oligodendroglioma, etc); provided IDH mutation data; and contained survival analysis data. Letters, comments, editorials, case reports, proceedings, and personal communications were excluded, as were studies in which no survival analysis was performed. Studies were identified by the search strategy by 2 independent reviewers. When there was uncertainty regarding eligibility, a third reviewer was consulted.

The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of participants in each group, participants’ age and sex, diagnostic criteria, tumor type and World Health Organization (WHO) grade, treatments, and survival data.

Quality Assessment

The quality of the included studies was assessed using the modified 18-items Delphi checklist, which is designed for assessing the quality of single-arm clinical studies.24 The quality assessment was also performed by 2 independent reviewers, and a third reviewer was consulted for any uncertainties.

Outcome Measures and Data Analysis

Overall survival and PFS were used to evaluate the association of IDH1 and IDH1/2 mutations, and prognosis for patients with malignant brain tumors. Hazard ratios (HRs) with corresponding 95% confidence intervals (CIs) for OS and PFS were calculated and compared between patients with and without mutations. Pooled HRs and 95% CIs were calculated for all studies combined, and for given subgroups (e.g., IDH mutation type or surgery vs no surgery). A HR value <1 indicates that mutations may prolong OS or PFS, whereas a HR value >1
| Study Characteristics | Diagnosis of Malignant Progression | Number of Patients | Age, y | Men, % | Tumor Type | WHO Tumor Grade | Treatments | Time-point for Evaluation of OS and PFS |
|-----------------------|-----------------------------------|--------------------|--------|--------|------------|----------------|------------|--------------------------------------|
| Cairncross (2014)     | Retrospective Histological         | 291                | ≥18    | 60     | Anaplastic oligodendroglia, anaplastic oligoastrocytoma | II, III | CHT, RT | n/a                                  |
| Hatanpaa (2014)       | Retrospective High nestin protein expression is a strong adverse prognostic factor | 50 | Median = 37.5 (range 20–66) | 52 | Astrocytomas, oligodendroglia, oligoastrocytoma | II, III | Surgery, CHT, RT | After diagnosis |
| Polivka (2014)        | Retrospective Neomorphic function of the mutated enzyme | 44 | Median = 64.3 (range 35–87) | 50 | Glioblastoma | IV | Surgery, CHT | Time after diagnosis |
| Frenel (2013)         | Retrospective n/a | 43 | Median = 51 (range 25–78) | 65 | Anaplastic oligodendroglia | n/a | Surgery, CHT, RT | Time after diagnosis |
| Gorlia (2013)         | Retrospective Signs of clinical or radiological progression | 368 | Median = 49.5 (range 18.6–68.7) | 57.6 | Oligodendroglia or oligoastrocytoma | n/a | RT, RT + CHT | OS: the time from randomization until death regardless of cause PFS: time from randomization until clinical or radiological progression or death |
| Ohno (2013)           | Retrospective Histopathologically progressed from lower-grade gliomas | 18 | Median = 30.5 (range 20–64) | 66.7 | Diffuse astrocytoma, anaplastic astrocytoma, anaplastic oligodendroglia, anaplastic oligoastrocytoma | II, III | Surgery | n/a |
| Yao (2013)            | Retrospective n/a | 53 | Mean = 39.5, median = 38 (range 5–67) | 54.7 | Gliomas | II (n = 29), III (n = 16), IV (n = 8) | CHT, surgery | OS: time between the diagnosis and death or last follow-up PFS: the time between the diagnosis and first unequivocal clinical or radiological sign of progressive disease |
| Ahmadi (2012)         | Retrospective Malignant progression towards anaplastic astrocytomas of WHO grade III and secondary glioblastomas | 100 | Median = 37 (range 19–72) | 55 | WHO grade II astrocytomas | II | Surgical resection or biopsy, RT, CHT | Time first symptoms appeared |
| Jurafli (2012)        | Retrospective n/a | 99 | Mean = 37.5 | 55.6 | Oligodendroglia or oligoastrocytoma | II (n = 1), III (n = 64), diffuse astrocytomas (n = 64) | CHT, RT | OS: time interval from LGG diagnosis to death or censor. Secondary PFS: the time between first diagnosis of a HGG and first tumor recurrence or tumor progression |
| Leibetseder (2013)    | Retrospective MRI | 47 | Median = 32 (range 18–39) | 59.5 | GBM | n/a | Surgery, CHT, RT | Time after surgery |
| Mukana (2012)         | Retrospective | 250 | Range 12-80 | 40–100 | GBM (glioblastoma) primary grade IV, 109 (43%); GBM secondary (grade IV), 13 (5.2%); GBM secondary (grade IV), 3 (1.2%); anaplastic astrocytoma (grade III), 29 (11.6%); anaplastic oligoastrocytoma (grade III), 5 (2%); anaplastic oligodendroglia (grade III), 15 (6%); diffuse astrocytoma (grade II), 29 (11.6%); oligoastrocytoma (grade II), 7 (2.8%); oligodendroglia (grade II), 25 (1%); pilocytic astrocytoma (grade I), 9 (3.6%); ganglioglioma (grade I), 6 (2.4%) | I, IV | Surgical resection | From date of surgical procedure |
| 1st Author (y) | Type of Study | Diagnosis of Malignant Progression | Number of Patients | Age, y | Men, % | Tumor Type | WHO Tumor Grade | Treatments | Time-point for Evaluation of OS and PFS |
|---------------|---------------|-----------------------------------|--------------------|--------|--------|------------|----------------|------------|------------------------------------------|
| Thon (2012)   | Retrospective | Multilocular tumor appearance/contrast enhancement of an initially nonenhancing lesion combined with rapid tumor growth | 127 | Median = 37.0 (range 18.0–75.0) | 47 | Astrocytoma: fibrillary astrocytoma, 118 (93%); gemistocytic astrocytoma, 8 (6.2); protoplasmic astrocytoma, 1 (0.78%) | II | RT, CHT, surgery | From date of first surgical procedure |
| Okita (2012)  | Retrospective | MRI (Gd-DTPA) showed a new enhancing lesion | 72 | Median = 39 (range 21–75) | 55.6 | Gliomas | II | CHT, RT, surgery | After surgery |
| SongTao (2012)| Retrospective | >25% increase in T2 hypointensity or contrast enhancement, or tumor-related neurologic deterioration | 86 | Median = 40 (range 20–72) | 54.7 | Astrocytoma, oligoastrocytoma, anaplastic astrocytoma, anaplastic oligoastrocytoma | Low-grade glioma | CHT | After diagnosis |
| Takano (2012) | Retrospective | n/a | 164 | Mean = 48.6 ± 14.3 (range 18–83) | Male predominant | n/a | Grade IV | glioblastomas, 52 (41 primary, 11 secondary); grade II, 46 (42 diffuse astrocytomas, 4 oligodendrogliomas) | n/a | CHT, RT, surgery | After surgery |
| II, III, IV   | Primary surgery | Time of surgery | n/a | Median = 36.7 (range 17.4–75.7) | 67.4 (cohort A); 58 (cohort B) | Diffuse astrocytoma, mixed oligoastrocytoma, oligodendroglioma | II | Surgical resection, no CHT, no RT (cohort A), RT, CHT, surgical resection (cohort B) | From day of initial surgery |
| Hartmann (2013)| Cohort       | n/a | 89 (cohort A); 30 (cohort B) | Median = 36.7 (range 17.4–75.7) | 67.4 (cohort A); 58 (cohort B) | Diffuse astrocytoma, mixed oligoastrocytoma, oligodendroglioma | II | Surgical resection, no CHT, no RT (cohort A), RT, CHT, surgical resection (cohort B) | From day of first surgery |
| Ohka (2011)   | Retrospective | n/a | 57 (grade 2 glioma) 54 (GBM) | Median = 42.0 (range 21–72) for grade 2 glioma; median = 59.0 (range 12–84) for GBM | 63 (grade 2 glioma); 61 (GBM) | Astrocytoma, oligodendroglioma, oligo-astrocytoma (grade II glioma), primary GBM, secondary GBM | II | CHT, RT, surgery | From day of initial surgery |
| SongTao (2011)| Retrospective | >25% increase in T2 hypointensity or contrast enhancement, or tumor-related neurologic deterioration | 203 | Median = 36.4 (range 2–78) | 55.7 | Pleomorphic astrocytoma, ganglioglioma, diffuse astrocytoma, oligodendroglioma, oligoastrocytoma, anaplastic astrocytoma, anaplastic oligoastrocytoma, anaplastic oligodendroglioma, primary glioblastoma, secondary glioblastoma | n/a | CHT, RT, surgery | After surgery |
| Blecker (2010)| Retrospective | n/a | 98 | Mean = 58 for no mutation; mean = 41 for mutation | 54.1 | n/a | n/a | CHT, RT, surgery | After surgery |
indicates the absence of mutations may decrease OS or PFS. A HR value equal to 1 indicates there was no significant association of IDH1 or IDH1/2 mutations with OS or PFS.

Heterogeneity among the studies was evaluated by the Cochran Q and the I² statistic. A Q statistic, with a P < 0.10, was considered to indicate statistically significant heterogeneity. The I² statistic indicates the percentage of the observed between-study variability due to heterogeneity rather than chance, and a value >50% was considered to indicate significant heterogeneity. Random-effects models (DerSimonian–Laird method) were used if heterogeneity was detected (I² > 50% or Q statistics P < 0.1). Otherwise, fixed-effects models (Mantel–Haenszel method) were utilized. Sensitivity analysis was performed using the leave-one-out approach. Publication bias was assessed by constructing funnel plots and by Egger test. The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution, and a 1-tailed significance level of P > 0.05 (Egger test). All statistical assessments were 2-sided, and a value of P < 0.05 was considered as statistically significant. Statistical analyses were performed using the statistical software Comprehensive Meta-Analysis, version 2.0 (Biostat, Englewood, NJ).

RESULTS

Search Results and Study Characteristics

A flow diagram of study selection is shown in Figure 1. A total of 165 studies were identified in the database search. After a review of the abstracts, 136 studies were excluded because they did not match the topic of the current analysis. Thus, 29 full-text articles were assessed for eligibility, and of these, 5 were excluded as they did not provide a quantitative outcome. Therefore, 24 studies were included in the qualitative synthesis. The characteristics and populations of the included studies are summarized in Table 1, and OS and PFS data are summarized in Table 2. Studies that reported median OS or PFS time were not considered for the analysis because most of the included studies were presented as HR. The study by Mukasa et al was not included in the analysis because the HRs were reported by tumor stage.

Association of IDH1 or IDH2 Mutations With OS

A total of 15 studies with completed data of OS were included in the analysis. Significant heterogeneity was noted (I² = 59.23%, Q statistic = 34.336, P = 0.002); therefore, a random-effects model was used. The pooled HR of 0.358 (95% CI 0.248–0.487, P < 0.001) indicated that IDH1 or IDH1/2 mutations were associated with better OS (Figure 2). When patients were stratified by surgery versus no surgery or IDH1 versus IDH1/2 mutations, the results also indicated that the presence of IDH mutations was associated with better OS.

Association of IDH1 or IDH2 Mutations With PFS

A total of 10 studies with completed data of PFS were included in the analysis. Significant heterogeneity was noted (I² = 53.53%, Q statistic = 19.369, P = 0.022); therefore, a random-effects model was used. The pooled HR of 0.322 (95% CI 0.248–0.487, P < 0.001) indicated that IDH1 or IDH1/2 mutations were associated with better PFS (Figure 3). When patients were stratified by surgery versus no surgery or IDH1 versus IDH1/2 mutations, the results also indicated that the presence of IDH mutations was associated with better PFS.
| 1st Author (y) | IDH Mutation | Number of Patients | Surgery | Mutation Rate (%) | Hazard Ratio (95% CI) for OS | Hazard Ratio (95% CI) for PFS |
|----------------|-------------|--------------------|---------|-------------------|-----------------------------|-----------------------------|
| Cairncross (2014) | IDH1/IDH2 | 291 | No | 74 | 0.41 (0.27–0.63) ref. no mutation | n/a |
| Hatanpaa (2014) | IDH1/IDH2 | 50 | Yes | 84 | RR = 6.99 (1.91–25.66) ref. mutation | n/a |
| Polivka, (2014) | IDH1 | 44 | Yes | 45 | Median: 270 d (139–400) mutant/ 130 d (87–172) wild type | n/a |
| Frenel (2013) | IDH1/IDH2 | 43 | No | 54 | 0.1 (0–0.7) ref. no mutation | 0.1 (0–0.3) ref. no mutation |
| Gorlia (2013) | IDH1/IDH2 | 368 | No | 45.6 | 0.478 (0.334–0.682) ref. no mutation | 0.422 (0.291–0.610) ref. no mutation |
| Ohno (2013) | IDH1/IDH2 | 18 | Yes | 44.4 | Wild-type IDH1: 2, 6.8 vs mutant IDH1: 2, 6.75 mo: P = 0.93 | n/a |
| Yao (2013) | IDH1 | 53 | Yes | 60.4 | 4.74 (1.73–12.98) ref. Mutation | 3.60 (1.45–8.95) ref. mutation |
| Ahmadi (2012) | IDH1 | 100 | Yes | 79 | Median 81.4 (range 5.5–274.8) mutation; median 80.2 (range 12.4–192) wild type | Median 44.6 (range 1–267) mutation; median 67.4 (range 7.9–116.9) wild type |
| Juratli (2012) | IDH1/IDH2 | 99 | No | 75.7 | 0.5 (0.3–0.9) ref. no mutation | 0.5 (0.3–0.8) ref. no mutation |
| Leibetseder (2012) | IDH1 | 47 | Yes | 43.4 | Median 28 mo (24–31.6) | Median 12 m (9.5–14) |
| Mukasa (2012) | IDH1/IDH2 | 250 | Yes | II: 65.6; III: 44; primary GBM: 5.5 | Grade II: 0.329 (0.0728–1.5270); grade III: 0.319 (0.0985–0.9519); primary GBM: 0.905 (0.269–2.4203) | Grade II: 0.602 (0.1678–2.1535) ref. no mutation; grade III: 0.059 (0.0086–0.2395) ref. no mutation; primary GBM: 0.898 (0.2575–2.4255) |
| Thon (2012) | IDH1 | 127 | Yes | 78 | 1.30 (0.72–2.33) ref. mutation | 2.17 (1.26–3.74) ref. mutation |
| Okita (2012) | IDH1/IDH2 | 72 | Yes | 58.3 | 0.365 (0.155–0.819) ref. no mutation | 0.558 (0.289–1.068) ref. no mutation |
| SongTao (2012) | IDH1/IDH2 | 86 | No | 73.4 | HR = 0.110, P ≤ 0.001 | HR = 0.110, P ≤ 0.001 |
| Takano (2012) | IDH1 | 164 | Yes | 47.3 | 0.256 (0.068–0.959) adjusted | 0.088 (0.023–0.333) adjusted |
| Hartmann (2011) | IDH1 | 89 | Yes | 81.8 | Cohort A: mutated median 10.5 y (5.1–15.9) Cohort B: mutated median 50.0 y (0–100) | Cohort A: 4.5 (4.0–5.1); cohort B: 6.7 (1.6–11.7) |
| Ohka (2011) | IDH1/IDH2 | 57 grade 2 glioma; 54 GBM | Yes | 82.4 | 6.433 (0.522–79.280) ref. mutation | 1.886 (0.571–6.886) ref. mutation |
| SongTao (2011) | IDH1/IDH2 | 203 | Yes | 41 | IDH mutant: median 57.34 mo; IDH wild type: median 21.30 mo | IDH mutant: median 56.87 mo IDH wild type: median 13.70 mo |
| Bleeker (2010) | IDH1 | 98 | Yes | 18 | 0.209 (0.093–0.471) ref. no mutation | n/a |
| Christensen (2010) | IDH1/IDH2 | 131 | No | 60 | 0.27 (0.10–0.72) ref. no mutation | n/a |
| Houllier (2010) | IDH1/IDH2 | 271 | No | 69.8 | HR = 0.32, P = 0.003 | HR = 0.92, P = 0.7 |
| Metellus (2010) | IDH1/IDH2 | 47 | No | 85 | 40.9 (2.89–578.49) ref. mutation | 6.79 (2.12–21.77) ref. mutation |
| van den Bent (2010) | IDH1/IDH2 | 159 | No | 45.9 | 0.24 (0.15–0.38) ref. no mutation | 0.27 (0.18–0.40) ref. no mutation |
| Kim (2010) | IDH1/IDH2 | 360 | Yes | 89.2 | 1.047 (0.593–1.850) ref. mutation | n/a |

CI = confidence interval, GBM = glioblastoma multiforme, HR = hazard ratio, IDH = isocitrate dehydrogenase, n/a = not available, ref. = reference group.
Sensitivity Analysis

Results of the sensitivity analysis using the leave-one-out approach for OS and PFS are shown in Figure 4. For both OS and PFS, the pooled estimates with each of the studies removed in turn remained statistically significant, indicating that the meta-analysis had good reliability for both measures (HRs for OS: range 0.33–0.38, all P values < 0.001; HRs for PFS, range 0.31–0.37, all P values < 0.001).

Publication Bias Analysis

Results of the evaluation of publication bias for OS and PFS are shown in Figure 5. For both measures, the funnel plots were symmetric (both P < 0.001; classic fail-safe test). However, Egger test indicated that the intercepts of the funnel plots did not obtain statistical significance (OS: 1-tailed, P = 0.037; PFS: 1-tailed, P = 0.075, respectively). Hence, publication bias may exist with respect to OS.

Quality Assessment

Results of the quality assessment using the modified 18-item Delphi checklist are shown in Table 3. All of the included studies clearly stated the aim of the study in the abstract or introduction, and described the characteristics of the included participants. The eligibility criteria of all the studies were explicit and appropriate, and outcome measures were all well-defined. The final total Delphi checklist scores of the studies ranged from 9 to 15 (maximum possible score of 18). Overall, the results indicate the studies are of good quality.
DISCUSSION

The purpose of this meta-analysis was to evaluate the prognostic value of IDH1/2 mutations with respect to OS and PFS in patients with glioblastoma. The results showed that the presence of IDH1/2 mutations was associated with longer OS and PFS, and this result was seen in both patients treated with surgery and those treated nonsurgically (e.g., radiotherapy), as well as in patients with IDH1 and IDH1/2 mutations.

IDH1 mutations have been reported in secondary GBM, diffuse astrocytoma, oligodendrogliomas, anaplastic astrocytomas, anaplastic oligodendrogliomas, and anaplastic oligoastrocytomas, and rarely in primary GBM, and have not been reported in pilocytic astrocytoma, ependymoma, and medulloblastoma.43 Mutations have also been reported in other cancers including acute myeloid leukemia and colorectal and prostate cancer.43

Prior studies have found that IDH1/2 mutations may influence the prognosis of patients with secondary or greater than grade II gliomas; however, these studies have differed in design and the results have not always been consistent.16–21,44

Evidence has generally shown that IDH1 mutations are associated with improved OS and PFS, particularly in patients with high-grade gliomas.9,13,27 The prognostic value in low-grade gliomas is, however, less clear. For example, Sanson et al19 showed that the IDH1 mutation had a significant prognostic value for OS in gliomas, whereas Kim et al18 reported the IDH1/IDH2 mutation was of no prognostic value in 360 low-grade gliomas. Interestingly, although IDH1 mutations have generally been shown to be a prognostic indicator, their presence is not necessarily predictive of response to therapy.9,13,19,40 Reasons for these findings may have to do with the association of IDH1 mutations with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status.42 For example, Molenaar et al45 reported that the combination of IDH1 mutations and MGMT methylation status predicted survival in patients with glioblastomas better than either IDH1 or MGMT status alone. Though the reasons for the associations between survival and IDH1 and MGMT methylation status remain to be determined, it has been suggested there may be mechanistic link between IDH1 mutations and MGMT methylation.46

Prior studies have suggested that chemoradiotherapy may be effective for a subset of patients with gliomas, as the addition of procarbazine, lomustine, and vincristine (PCV) chemotherapy to radiotherapy conferred a significant increase in OS and PFS.47,48 Among the studies included in the current analysis, Okita et al28 suggested IDH1/2 mutations were predictive for response to chemoradiotherapy, but not radiotherapy alone in patients with grade II gliomas. However, van den Bent et al13
FIGURE 5. Evaluation of publication bias by funnel plot and the Egger test for (A) overall survival (OS) and (B) progression-free survival (PFS).
| 1st Author /Publication Year | Cairncross (2014) | Hatanpaa (2014) | J. Polivka (2014) | Frenel (2013) | Gorlia (2013) | Yoo (2013) | Yoo (2012) | Yoo (2012) | Leibetseder (2012) | Niklas (2012) | Okita (2012) | SongTao (2012) | Takano (2012) | Hartmann (2011) | Ohka (2011) | SongTao (2011) | Blecher (2010) | Christensen (2010) | Houllier (2010) | Metellus (2010) | van den Bent (2010) | Kim (2010) |
|-----------------------------|------------------|-----------------|------------------|---------------|--------------|-------------|------------|------------|------------------|--------------|-------------|----------------|--------------|----------------|-------------|----------------|----------------|------------------|----------------|----------------|-----------------|-------------|
| Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Are the characteristics of the participants included in the study described? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Unknown | Y |
| Were the cases collected in more than 1 center? | Y | N | Y | N | N | N | N | N | N | N | N | N | N | N | Y | N | N | N | N |
| Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Were participants recruited consecutively? | N | N | N | N | Y | Y | N | Unknown | N | Y | N | Y | N | N | N | N | N | N | N | N | N | N |
| Did participants enter the study at a similar point in the disease? | N | N | N | N | Y | Y | N | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Unknown | N | Y | N | N |
| Was the intervention clearly described in the study? | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Were additional interventions (counterinterventions) clearly reported in the study? | Y | Y | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Was the outcome measure clearly defined in the introduction or methods section? | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y | Y |
| Were relevant outcomes appropriately measured with objective and/or subjective methods? | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Were outcomes measured before and after intervention? | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Were the statistical tests used to assess the relevant outcomes appropriate? | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |
| Was the length of follow-up reported? | Y | Y | Y | Y | N | Y | Y | Y | Y | N | N | Y | Y | Y | Y | Y | N | Y | N | N | N | N |
| Was the loss to follow-up reported? | N | N | N | N | N | Y | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N | N |

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.
reported that IDH1 mutations were predictive of both OS and PFS for patients treated with radiotherapy and radiotherapy/PVC. It has also been reported that patients with low-grade gliomas were sensitive to temozolomide. In the current meta-analysis, we did not evaluate the predictive value of IDH1/2 mutations with respect to radiotherapy, chemotherapy, or chemoradiotherapy. This was due to the heterogeneity across the studies, and because few studies directly evaluated this question.

Other prior meta-analyses have evaluated the association of IDH mutations and survival in patients with glioblastomas. An analysis by Cheng et al included 9 studies with a total of 1669 patients with glioblastomas, and, similar to our results, found that IDH1 mutations were associated with improved OS. Zou et al performed a meta-analysis including 12 studies with a total of 2190 patients, and reported HRs for OS and PFS in patients with IDH mutations were 0.33 (95% CI 0.25–0.42) and 0.38 (95% CI 0.21–0.68), respectively, as compared with glioma patients with the wild-type IDH gene. Subgroup analyses based on tumor grade also showed that the presence of IDH mutations was associated with better outcomes.

There are several limitations to this analysis that should be considered when interpreting the results. We did not evaluate whether the histological subtype or tumor grade influenced the association of IDH1/2 mutations with the survival outcomes of patients with secondary GBM. As mentioned above, we also did not evaluate whether the type of treatment regimen influenced the prognostic value of IDH1/2 mutations of patients with secondary GBM. Furthermore, significant heterogeneity was present among the studies for both OS and PFS with respect to tumor type and grade, treatments, method for calculating end-points, and method for determining the presence of mutations. Publication bias may be present as well, for those studies without significance might not be submitted or published.

CONCLUSIONS

In summary, the results of this meta-analysis indicate that IDH1/2 mutations are associated with improved survival in patients with glioblastomas.

REFERENCES

1. Urbańska K, Sokołowska J, Szmidi M, et al. Glioblastoma multiforme: an overview. Contemp Oncol (Poln). 2014;18:307–312.
2. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013;19:764–772.
3. Bleeker FE, Atai NA, Lamba S, et al. The prognostic IDH1 (R132) mutation is associated with reduced NADP+-dependent IDH activity in glioblastoma. Acta Neuropathol. 2010;119:487–494.
4. Guo C, Pirozzi CJ, Lopez GY, et al. Isocitrate dehydrogenase mutations in gliomas: mechanisms, biomarkers and therapeutic target. Curr Opin Neurol. 2011;24:648–652.
5. Alexander BM, Mehta MP. Role of isocitrate dehydrogenase in glioma. Expert Rev Neurother. 2011;11:1399–1409.
6. Koschland DE Jr, Walsh K, LaPorte DC. Sensitivity of metabolic fluxes to covalent control. Curr Top Cell Regul. 1985;27:13–22.
7. Geisbrecht BV, Gould SJ. The human PICD gene encodes a cytoplasmic and peroxisomal NADP+-dependent isocitrate dehydrogenase. J Biol Chem. 1999;274:30527–30533.
8. Margiotta E, Banhegyi G. Isocitrate dehydrogenase: a NADPH-generating enzyme in the lumen of the endoplasmic reticulum. Arch Biochem Biophys. 2008;471:184–190.
9. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360:765–773.
10. Balss J, Meyer J, Mueller W, et al. Analysis of the IDH1 codon 132 mutation in brain tumors. Acta Neuropathol. 2008;116:597–602.

11. Ichimura K, Pearson DM, Kocialkowski S, et al. IDH1 mutations are present in the majority of common adult gliomas but rare in primary glioblastomas. Neuro Oncol. 2009;11:341–347.

12. Hartmann C, Meyer J, Balss J, et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendrogial differentiation and age: a study of 1,010 diffuse gliomas. Acta Neuropathol. 2009;118:469–474.

13. van den Bent MJ, Dubinkin HJ, Marie Y, et al. IDH1 and IDH2 mutations are prognostic but not predictive for outcome in anaplastic oligodendrogial tumors: a report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. Clin Cancer Res. 2010;16:1597–1604.

14. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462:739–744.

15. Baldepsersd Tewarie NM, Burgers IA, Dawood Y, et al. NADP+-dependent IDH1 R132 mutation and its relevance for glioma patient survival. Med Hypotheses. 2013;80:728–731.

16. Mettus P, Coulhaly B, Colin C, et al. Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis. Acta Neuropathol. 2010;120:719–729.

17. Houillier C, Wang X, Kaloshi G, et al. IDH1 or IDH2 mutations predict longer survival and response to temozolomide in low-grade gliomas. Neurology. 2010;75:1560–1566.

18. Kim YH, Nobusawa S, Mittelbronn M, et al. Molecular classification of low-grade diffuse gliomas. Am J Pathol. 2010;177:2708–2714.

19. Sanson M, Marie Y, Paris S, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol. 2009;27:4150–4154.

20. Nobusawa S, Watanabe T, Kleihues P. IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. Clin Cancer Res. 2009;15:6002–6007.

21. Mukasa A, Takayangi S, Saito K, et al. Significance of IDH mutations varies with tumor histology, grade, and genetics in Japanese glioma patients. Cancer Sci. 2012;103:587–592.

22. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151:W65–W94.

23. Sullivan GM. Irb 101. J Grad Med Educ. 2011;3:5–6.

24. Moga C, Guo B, Schopflocher D, et al. Development of a Quality Appraisal Tool for Case Series Studies Using a Modified Delphi Technique. Edmonton AB: Institute of Health Economics; 2012.

25. Yao Y, Chan AK, Qui ZY, et al. Mutation analysis of IDH1 in paired gliomas revealed IDH1 mutation was not associated with malignant progression but predicted longer survival. PLoS One. 2013;8:e67421.

26. Gorlia T, Kirsch M, Geiger K, et al. The prognostic value of IDH mutations and MGMT promoter methylation in secondary high-grade gliomas. J Neurooncol. 2012;110:325–333.

27. Juratli TA, Kirsch M, Geiger K, et al. The prognostic value of IDH1/2 mutation is a prognostic marker for survival and predicts response to chemotherapy for grade II gliomas concomitantly treated with radiation therapy. Int J Oncol. 2012;41:1325–1336.

28. Okita Y, Narita Y, Miyakita Y, et al. IDH1/2 mutation is a prognostic marker for survival and predicts response to chemotherapy for grade II gliomas concomitantly treated with radiation therapy. Int J Oncol. 2012;41:1325–1336.

29. Ohita F, Natsume A, Motomura K, et al. The global DNA methylation surrogate LINE-1 methylation is correlated with MGMT promoter methylation and is a better prognostic factor for glioma. PLoS One. 2011;6:e23332.

30. Hartmann C, Hentschel B, Tatagiba M, et al. Molecular markers in low-grade glioma: predictive or prognostic? Clin Cancer Res. 2011;17:4588–4599.

31. Ahmadi R, Stockhammer F, Becker N, et al. No prognostic value of IDH1 mutations in a series of 100 WHO grade II astrocytomas. J Neurooncol. 2012;109:15–22.

32. Takano S, Kato Y, Yamamoto T, et al. Immunohistochemical detection of IDH1 mutation, p53, and interxin as prognostic factors of glial tumors. J Neurooncol. 2012;108:361–373.

33. Cairncross JG, Wang M, Jenkins RB, et al. Benefit from procarbazine, lomustine, and vincristine in oligodendrogial tumors is associated with mutation of IDH1. J Clin Oncol. 2014;32:783–790.

34. Hatanpaa KJ, Hu T, Vermeirey V, et al. High expression of the stem cell marker nestin is an adverse prognostic factor in WHO grade II-III astrocytomas and oligoastrocytomas. J Neurooncol. 2014;117:183–189.

35. Polivka J, Polivka J Jr, Rohan V, et al. Isocitrate dehydrogenase-1 mutations as prognostic biomarker in glioblastoma multiforme patients in West Bohemia. Biomed Res Int. 2014;2014:735659.

36. Thon N, Eigenbrod S, Keeth S, et al. IDH1 mutations in grade II astrocytomas are associated with unfavorable progression-free survival and prolonged postrecurrence survival. Cancer. 2012;118:452–460.

37. Frenel JS, Leux C, Loussouarn D, et al. Combining two biomarkers, IDH1/2 mutations and 1p/19q codeletion, to stratify anaplastic oligodendroglioma in three groups: a single-center experience. J Neurooncol. 2013;114:85–91.

38. Ohno M, Narita Y, Miyakita Y, et al. Secondary glioblastomas with IDH1/2 mutations have longer glioma history from preceding lower-grade gliomas. Brain Tumor Pathol. 2013;30:224–232.

39. Leibetseder A, Ackerl M, Flechl B, et al. Outcome and molecular characteristics of adolescent and young adult patients with newly diagnosed primary glioblastoma: a study of the Society of Austrian Neurooncology (SANO). Neuro Oncol. 2013;15:112–121.

40. SongTao Q, Lei Y, Si G, et al. IDH mutations predict longer survival and response to temozolomide in secondary glioblastoma. Cancer Sci. 2012;103:269–273.

41. SongTao Q, Yu L, Lu YT, et al. IDH mutations occur frequently in Chinese glioma patients and predict longer survival but not response to concomitant chemoradiotherapy in anaplastic gliomas. Oncol Rep. 2011;26:1479–1485.

42. Christensen BC, Smith AA, Zheng S, et al. DNA methylation, isocitrate dehydrogenase mutation, and survival in glioma. J Natl Cancer Inst. 2011;103:143–153.

43. Hodges TR, Choi BD, Bigner DD, et al. Isocitrate dehydrogenase 1: what it means to the neurosurgeon: a review. J Neurosurg. 2013;118:1176–1180.

44. Hartmann C, Hentschel B, Simon M, et al. Long-term survival in primary glioblastoma versus without isocitrate dehydrogenase mutations. Clin Cancer Res. 2013;19:5146–5157.

45. Molenaar RJ, Verbaan D, Lamba S, et al. The combination of IDH1 mutations and MGMT methylation status predicts survival in glioblastoma better than either IDH1 or MGMT alone. Neuro Oncol. 2014;16:1263–1273.

46. Wick W, Meisner C, Hentschel B, et al. Prognostic or predictive value of MGMT promoter methylation in gliomas depends on IDH1 mutation. Neurology. 2013;81:1515–1522.

47. van den Bent MJ, Brandes AA, Taphoorn MJ, et al. Adjuvant procarbazine, lomustine, and vincristine chemotherapy in newly
diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC Brain Tumor Group Study 26951. J Clin Oncol. 2013;31:344–350.

48. Cairncross G, Wang M, Shaw E, et al. A phase 3 trial of chemoradiotherapy for anaplastic oligodendroglioma: long term results of RTOG 9402. J Clin Oncol. 2013;31:337–343.

49. Cheng HB, Yue W, Xie C, et al. IDH1 mutation is associated with improved overall survival in patients with glioblastoma: a meta-analysis. Tumour Biol. 2013;34:3555–3559.

50. Zou P, Xu H, Chen P, et al. IDH1/IDH2 mutations define the prognosis and molecular profiles of patients with gliomas: a meta-analysis. PLoS One. 2013;8:e68782.