IDH1 Mutation and World Health Organization 2016 Diagnostic Criteria for Adult Diffuse Gliomas: Advances in Surgical Strategy

Kensuke Tateishi, MD, PhD[*‡§]
Hiroaki Wakimoto, MD, PhD[*§]
Daniel P. Cahill, MD, PhD[*§]

[*]Department of Neurosurgery, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts; [‡]Department of Neurosurgery, Graduate School of Medical Science, Yokohama City University, Yokohama, Japan; [§]Translational Neuro-Oncology Laboratory, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, Massachusetts

This work is based on "IDH Mutation and Glioma Surgery: Advances in Surgical Strategy," presented at the 2016 CNS Annual Meeting in San Diego, California.

Correspondence:
Daniel P. Cahill, MD, PhD,
Department of Neuosurgery,
Massachusetts General Hospital,
55 Fruit Street, Yawkey 9E,
Boston, MA 02114.
E-mail: cahill@mgh.harvard.edu.

Received, January 24, 2017.
Accepted, April 14, 2017.

The presence of an isocitrate dehydrogenase gene (*IDH1* or *IDH2)* mutation has become one of the most critical biomarkers for molecular classification and prognostication in adult diffuse gliomas.[1] Here, we review the translational impact of *IDH1/2* mutation on neurosurgical oncology, with a focus on how this emerging knowledge has advanced the precision of our surgical approach to these diseases.

Generally speaking, there are 2 major goals for the initial surgical procedure in a patient with suspected adult diffuse glioma. The first goal is to obtain sufficient tissue for diagnostic classification. In the era preceding the recent World Health Organization (WHO) 2016 revised criteria,[2] there were limitations on diagnosis imposed by surgical sampling error. In other words, the extent of surgery and subsequent diagnostic grading of an adult diffuse glioma had been shown to be tightly linked.[3,4] Patients who underwent biopsy only, unfortunately, would too often have inaccurate diagnoses, due to so-called undergrading, as there would be insufficient material for pathological review. This undergrading complicated the retrospective analyses of surgical treatment, since biopsy-only diagnoses were frequently inaccurate. However, with the molecular genomic component of classifiers codified into the revised diagnostic criteria (primarily *IDH1* mutation and 1p/19q-codeletion, as described below), this scenario has occurred more rarely,[5] since less tissue is required for molecular testing.

ABBREVIATIONS: 2-HG, 2-hydroxyglutarate; **GBM,** glioblastoma multiform; **IDH,** isocitrate dehydrogenase; **MGMT,** O6-methylguanine DNA-methyltransferase; **MRS,** magnetic resonance spectroscopy; **NADPH,** nicotinamide adenine dinucleotide phosphate; **NCF,** neurocognitive function; **NOS,** not otherwise specified; **OS,** overall survival; **PFS,** progression-free survival; **WHO,** World Health Organization

The second goal of surgery, in most cases, is to perform therapeutic cytoreduction to secure a prolonged survival and preservation of neurological function for the patient. For glioblastoma multiform (GBM), this has traditionally meant that "complete resection of enhancement" was the intended surgical goal,[6,7] while for lower grade lesions, which are mostly nonenhancing, this has meant "complete resection of T2/FLAIR hyper-intensity"[8] (Figure A). The evidence base that supports these surgical strategies requires updating in the context of the new WHO 2016 diagnostic criteria.

ETIOLOGY AND CLASSIFICATION FOR IDH MUTANT GLIOMAS

Recurrent mutations of the *IDH1* gene were initially identified in 12% of grade IV GBM within a broad sequence screen of more than 20,000 genes.[9] Subsequently, more focused large sample studies confirmed that *IDH1* mutation is found in the majority of secondary GBM, and only rarely found in primary GBM and GBM in children.[9-11] In addition, 50% to 80% of lower grade gliomas (categorized as grade II or III by the legacy WHO 2007 criteria) harbored *IDH1* mutation.[10-13] The *IDH1* gene mutation is almost always localized within exon 4 to codon 132 and >90% of alterations are c.395G>A (R132H) substitutions, followed by R132C as the second-most common alteration.[10,12,14] Although the frequency is rare, mutations in the homologous gene *IDH2* are also found in gliomas categorized as grade II or III by the legacy WHO 2007 criteria, and secondary GBM.[11,15] From a classification perspective, the discovery of *IDH1* mutation allows the clear distinction between primary GBM, which frequently harbors epidermal growth factor receptor, PTEN loss, and cyclin-dependent kinase inhibitor 2A (*CDKN2A*)

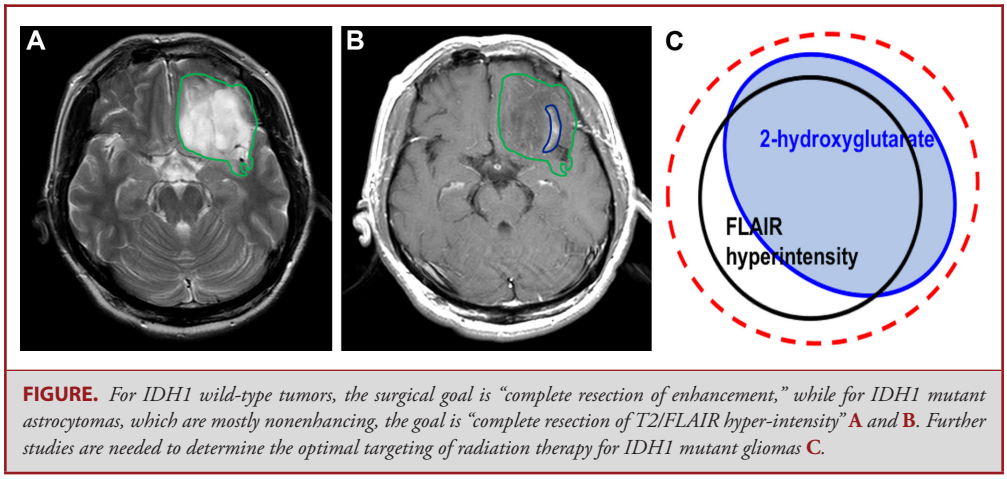

FIGURE. *For IDH1 wild-type tumors, the surgical goal is "complete resection of enhancement," while for IDH1 mutant astrocytomas, which are mostly nonenhancing, the goal is "complete resection of T2/FLAIR hyper-intensity"* **A** *and* **B**. *Further studies are needed to determine the optimal targeting of radiation therapy for IDH1 mutant gliomas* **C**.

gene, deletions, versus secondary GBM, which harbors *IDH1* mutation.[10,12,16,17]

With the revision of adult diffuse glioma classification, the 2016 WHO Classification of Tumors of the Central Nervous System integrated phenotypic and genotypic parameters.[2] For *IDH1* mutant gliomas, tumors are grouped as diffuse astrocytic or oligodendroglial tumors. This group was histologically and genetically divided based on the presence of *IDH* mutations (typically $IDH1^{R132}$ and $IDH2^{R172}$) and 1p/19q codeletion. As an additional reinforcement of this molecular classification, astrocytic gliomas containing *IDH1* mutation also near-universally contain *TP53* and *ATRX* gene mutation, whereas oligodendrogliomas are *IDH1* mutant with 1p/19q codeletion, often with concomitant *CIC* and *FUBP1* gene and *TERT* promoter mutation.[18,19] These co-occurring genetic abnormalities are mutually exclusive in the vast majority of cases.[18-22] Accordingly, most tumors are classified as follows: (1) diffuse astrocytoma (grade II) or anaplastic astrocytoma (grade III) or glioblastoma (grade IV); *IDH*-mutant, -wild type, or not otherwise specified (NOS); (2) oligodendroglioma (grade II) or anaplastic oligodendroglioma (grade III; *IDH* mutant and 1p/19q-codeleted or NOS). Remaining cases, which are *IDH1* wild type, are classified as (1) oligoastrocytoma (grade II), anaplastic oligoastrocytoma (grade III) (NOS); or (2) diffuse midline glioma (H3K27M-mutant). *IDH*-wild type glioblastoma (about 90% of cases) is known as primary GBM, while *IDH* mutant glioblastoma (about 10% of cases) corresponds to secondary GBM.[2]

PROGNOSTIC SIGNIFICANCE OF *IDH1* MUTATION IN GLIOMAS

In GBM, Parsons and colleagues[9] initially demonstrated that the overall survival (OS) in *IDH1*-mutant GBM was more than 3-fold longer than that in *IDH1* wild-type GBM. Independent groups rapidly replicated the finding that *IDH1* mutation is a favorable prognostic biomarker of both progression-free survival (PFS) and OS when compared to *IDH1* wild type in low-grade glioma and high-grade glioma.[11,13,23] Subsequently, the majority of clinical studies indicated that *IDH* mutation was an independent prognostic factor in grade II and III gliomas.[11,23-29] This evidence indicates that *IDH1* mutation is a favorable prognostic factor in adult gliomas. Among these studies, the prospective randomized study NOA-04 revealed *IDH1* mutation, hypermethylation of the O6-methylguanine DNA-methyltransferase (MGMT) promoter, age, extent of resection, and oligodendroglial histology are independent prognostic factors in anaplastic gliomas.[24] Of note, the impact of *IDH1* mutation conferred a stronger risk reduction than 1p/19q codeletion, *MGMT* promoter methylation, or histology.[24] In secondary high-grade gliomas, *IDH* mutations are also stronger prognostic markers of both PFS and OS than the *MGMT* promoter methylation status.[30] Notably, the prognosis of *IDH1* mutant GBM is better than anaplastic astrocytoma without *IDH1* mutation.[31] Taken together, *IDH1* mutation has proven to be a powerful prognostic factor in gliomas, irrespective of tumor grade and histology.

Additional clinical characteristics in the *IDH1* mutant gliomas are the tumor location and age distribution of the patients upon presentation. Compared with *IDH* wild type, *IDH1* mutant gliomas were predominantly located in the frontal lobe.[32-36] Patients with GBM or anaplastic astrocytoma with *IDH1* mutation were significantly younger than that with *IDH1* wild type.[9,11] Intriguingly, the patient age at diagnosis of grade II *IDH1* mutant astrocytoma is nearly identical grade III *IDH1* mutant anaplastic astrocytoma. Also, the age of *IDH1* mutant GBM was only 4 yr older than that of *IDH1* mutant grade II and III astrocytoma.[37] These findings highlighted the fact that grading, per se, had not been validated as a prognostic marker within the genomically homogeneous cohorts of *IDH1* mutant vs wild-type tumors, and serves as a cautionary note for future

analyses. Notably in this regard, Suzuki et al[29] classified gliomas that were grades II and III by WHO 2007 criteria on the basis of the presence of *IDH1* mutation, *TP53* mutation, and 1p/19q codeletion. Accordingly, tumors were classified into 3 groups: type I (*IDH1* mutant with 1p/19q codeletion; favorable prognostic group), type II (*IDH1* mutant with TP53 mutation; intermediate group), and type III (*IDH1* wild type; poor prognostic group).[29] Survival difference between grade II and grade III were observed only in type II (astrocytic), but not in type I (oligodendroglial) gliomas,[29] findings consistent with the results from large randomized studies of grade II and III oligodendrogliomas.[38,39]

TREATMENT EVIDENCE FOR *IDH1* MUTANT GLIOMAS

Although scant class I evidence exists, accumulating evidence supports the proposal that more extensive surgical resection has a pivotal role in improving survival in adults with glioma. Extensive resection has been demonstrated to be associated with a survival benefit in low-grade glioma and also in GBM (*IDH1* wild type).[6,8,40,41] Of note, magnetic resonance (MR) imaging studies have demonstrated *IDH1* mutant tumors to be rarely located in high-risk (so-called eloquent) areas of the brain, with a typically unilateral pattern of growth, sharp tumor margin, and less contrast enhancement,[32,42] implying *IDH1* mutant gliomas are relatively more feasible for resection, when compared to their wild-type counterparts. Intriguingly, patients with *IDH1* wild-type gliomas also display reduced neurocognitive function (NCF) and lower performance score than those with *IDH1* mutant gliomas.[43] In addition, glioma tumor volume was not associated with NCF for patients with *IDH1* mutant tumors, but was associated decreased NCF in *IDH1* wild-type tumors.[43] Diffusion-tensor imaging studies demonstrate that *IDH* mutant GBM have a less invasive phenotype compared to *IDH* wild-type lesions.[44] Interestingly, we found that extensive resection including nonenhancing area prolonged survival in *IDH1* mutant anaplastic astrocytoma and glioblastoma. Since *IDH1* mutant gliomas were predominantly located in frontal lobe and the less functional disturbance of adjacent normal brain, *IDH1* mutant gliomas were also more amenable to maximal resection.[35] These findings were consistent with an independent study, on a separate cohort, demonstrating that the gross total resection was associated with extended survival in grade III *IDH1* mutant gliomas without 1p/19q codeletion, but not in *IDH1* wild-type or *IDH1* mutant gliomas with 1p/19q codeletion.[45] Altogether, these findings suggest that extensive resection of both *enhancing* and *nonenhancing* (T2/FLAIR hyperintense) disease should be considered for *IDH1* mutant gliomas, especially astrocytoma, regardless of WHO grade[46] (Figure A and B).

To assess for mutant *IDH1* noninvasively, several MR techniques including diffusion tensor imaging, relative cerebral blood volume, and magnetic resonance spectroscopy (MRS) have been reported.[47-49] MRS can detect 2-hydroxyglutarate (2-HG), which is produced by the IDH mutant enzyme product and is found at levels 100-fold higher in tumors, than that of normal brain.[50-58] Additionally, intraoperative technologies to rapidly assess for *IDH1* mutation have been established.[59-61] Advances in these technologies may allow the surgical strategy to determine the degree of resection to be adjusted intraoperatively during a surgical procedure, based on the *IDH1* mutation status of the tumor.

Although there is no level I evidence that radiation therapy extends survival in glioma patients with *IDH1* mutation, experimental investigations have revealed that forced *IDH1* mutant expression in glioma cells results in increased reactive oxygen species, by inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) production, which promotes sensitivity to radiation therapy.[62-64] Indeed, 65% of the total NADPH production capacity in GBM is provided for by wild-type IDH activity and introduction of the *IDH1* mutation reduced this capacity by 38%.[65] In addition, MRS demonstrated that *IDH1* mutation decreased glutathione level compared with those with *IDH1* wild type.[51] Intriguingly, in *ATRX* mutant tumors, nonhomologous end joining was impaired and increased sensitivity to DNA damaging agents that induce double-stranded DNA breaks.[66] These findings may support the recent clinical data that patients with *IDH* mutant, 1p/19q non-codeleted (astrocytic) tumors treated with radiotherapy had a longer PFS than those treated with temozolomide, whereas no differences in PFS for patients with *IDH* mutant, 1p/19q codeleted (oligodendroglial), and *IDH* wild-type (GBM-like) tumors.[67] Recently, MRS detected 2-HG has been piloted in the clinical assessment of treatment response and treatment planning in radiotherapy,[56,68,69] indicating the potential for clinical application of noninvasively assessed 2-HG. Further work is needed to determine the optimal targeting of radiation therapy for *IDH1* mutant gliomas (Figure C).

CONCLUSION

In conclusion, with the revision of the WHO diagnostic criteria, surgery for adult diffuse gliomas has become even more tightly integrated with radiology and pathology, in both the diagnostic phase as well as the treatment phase of these diseases. Certain cases, namely *IDH1* mutant astrocytic gliomas, display a substantial survival benefit in association with maximal resection, regardless of tumor grade under the legacy criteria. Thus, individualization of surgical strategy for patients with *IDH1* mutant gliomas has advanced significantly in the modern era.

Disclosures

This work was supported by NIH P50CA165962 and Burroughs-Wellcome CAMS # 1007616.02. The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES

1. Dunn GP, Andronesi OC, Cahill DP. From genomics to the clinic: biological and translational insights of mutant IDH1/2 in glioma. *Neurosurgical Focus*. 2013;34(2):E2.
2. Louis DN, Perry A, Reifenberger G, et al. The 2016 world health organization classification of tumors of the central nervous system: a summary. *Acta Neuropathol*. 2016;131(6):803-820.
3. Glantz MJ, Burger PC, Herndon JE, 2nd, et al. Influence of the type of surgery on the histologic diagnosis in patients with anaplastic gliomas. *Neurology*. 1991;41(11):1741-1744.
4. Jackson RJ, Fuller GN, Abi-Said D, et al. Limitations of stereotactic biopsy in the initial management of gliomas. *Neuro Oncol*. 2001;3(3):193-200.
5. Kim BY, Jiang W, Beiko J, et al. Diagnostic discrepancies in malignant astrocytoma due to limited small pathological tumor sample can be overcome by IDH1 testing. *J Neurooncol*. 2014;118(2):405-412.
6. Lacroix M, Abi-Said D, Fourney DR, et al. A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *J Neurosurg*. 2001;95(2):190-198.
7. Stummer W, Reulen HJ, Meinel T, et al. Extent of resection and survival in glioblastoma multiforme: identification of and adjustment for bias. *Neurosurgery*. 2008;62(3):564-576; discussion 564-576.
8. Smith JS, Chang EF, Lamborn KR, et al. Role of extent of resection in the long-term outcome of low-grade hemispheric gliomas. *J Clin Oncol*. 2008;26(8):1338-1345.
9. Parsons DW, Jones S, Zhang X, et al. An integrated genomic analysis of human glioblastoma multiforme. *Science*. 2008;321(5897):1807-1812.
10. 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(4):341-347.
11. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. *N Engl J Med*. 2009;360(8):765-773.
12. Balss J, Meyer J, Mueller W, Korshunov A, Hartmann C, von Deimling A. Analysis of the IDH1 codon 132 mutation in brain tumors. *Acta Neuropathol*. 2008;116(6):597-602.
13. Nobusawa S, Watanabe T, Kleihues P, Ohgaki H. IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. *Clin Cancer Res*. 2009;15(19):6002-6007.
14. Pusch S, Schweizer L, Beck AC, et al. D-2-Hydroxyglutarate producing neo-enzymatic activity inversely correlates with frequency of the type of isocitrate dehydrogenase 1 mutations found in glioma. *Acta Neuropathol Commun*. 2014;2:19. doi:10.1186/2051-5960-2-19.
15. Hartmann C, Meyer J, Balss J, et al. Type and frequency of IDH1 and IDH2 mutations are related to astrocytic and oligodendroglial differentiation and age: a study of 1,010 diffuse gliomas. *Acta Neuropathol*. 2009;118(4):469-474.
16. Nonoguchi N, Ohta T, Oh JE, Kim YH, Kleihues P, Ohgaki H. TERT promoter mutations in primary and secondary glioblastomas. *Acta Neuropathol*. 2013;126(6):931-937.
17. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. *Clin Cancer Res*. 2013;19(4):764-772.
18. Arita H, Narita Y, Fukushima S, et al. Upregulating mutations in the TERT promoter commonly occur in adult malignant gliomas and are strongly associated with total 1p19q loss. *Acta Neuropathol*. 2013;126(2):267-276.
19. Killela PJ, Reitman ZJ, Jiao Y, et al. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proc Natl Acad Sci USA*. 2013;110(15):6021-6026.
20. Jiao Y, Killela PJ, Reitman ZJ, et al. Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. *Oncotarget*. 2012;3(7):709-722.
21. Kannan K, Inagaki A, Silber J, et al. Whole-exome sequencing identifies ATRX mutation as a key molecular determinant in lower-grade glioma. *Oncotarget*. 2012;3(10):1194-1203.
22. Liu XY, Gerges N, Korshunov A, et al. Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. *Acta Neuropathol*. 2012;124(5):615-625.
23. 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(25):4150-4154.
24. Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. *J Clin Oncol*. 2009;27(35):5874-5880.
25. Sun H, Yin L, Li S, et al. Prognostic significance of IDH mutation in adult low-grade gliomas: a meta-analysis. *J Neurooncol*. 2013;113(2):277-284.
26. Killela PJ, Pirozzi CJ, Healy P, et al. Mutations in IDH1, IDH2, and in the TERT promoter define clinically distinct subgroups of adult malignant gliomas. *Oncotarget*. 2014;5(6):1515-1525.
27. Minniti G, Scaringi C, Arcella A, et al. IDH1 mutation and MGMT methylation status predict survival in patients with anaplastic astrocytoma treated with temozolomide-based chemoradiotherapy. *J Neurooncol*. 2014;118(2):377-383.
28. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. *N Engl J Med*. 2015;372(26):2499-2508.
29. Suzuki H, Aoki K, Chiba K, et al. Mutational landscape and clonal architecture in grade II and III gliomas. *Nat Genet*. 2015;47(5):458-468.
30. Juratli TA, Kirsch M, Geiger K, et al. The prognostic value of IDH mutations and MGMT promoter status in secondary high-grade gliomas. *J Neurooncol*. 2012;110(3):325-333.
31. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. *Acta Neuropathol*. 2010;120(6):707-718.
32. Lai A, Kharbanda S, Pope WB, et al. Evidence for sequenced molecular evolution of IDH1 mutant glioblastoma from a distinct cell of origin. *J Clin Oncol*. 2011;29(34):4482-4490.
33. Yan W, Zhang W, You G, et al. Correlation of IDH1 mutation with clinicopathologic factors and prognosis in primary glioblastoma: a report of 118 patients from China. *PLoS One*. 2012;7(1):e30339.
34. Ellingson BM, Lai A, Harris RJ, et al. Probabilistic radiographic atlas of glioblastoma phenotypes. *AJNR Am J Neuroradiol*. 2013;34(3):533-540.
35. Beiko J, Suki D, Hess KR, et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. *Neuro Oncol*. 2014;16(1):81-91.
36. Sun ZL, Chan AK, Chen LC, et al. TERT promoter mutated WHO grades II and III gliomas are located preferentially in the frontal lobe and avoid the midline. *Int J Clin Exp Pathol*. 2015;8(9):11485-11494.
37. Reuss DE, Mamatjan Y, Schrimpf D, et al. IDH mutant diffuse and anaplastic astrocytomas have similar age at presentation and little difference in survival: a grading problem for WHO. *Acta Neuropathol*. 2015;129(6):867-873.
38. Cairncross G, Berkey B, Shaw E, et al. Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. *J Clin Oncol*. 2006;24(18):2707-2714.
39. Buckner JC, Shaw EG, Pugh SL, et al. Radiation plus Procarbazine, CCNU, and vincristine in low-grade glioma. *N Engl J Med*. 2016;374(14):1344-1355.
40. Sanai N, Polley MY, McDermott MW, Parsa AT, Berger MS. An extent of resection threshold for newly diagnosed glioblastomas. *J Neurosurg*. 2011;115(1):3-8.
41. Marko NF, Weil RJ, Schroeder JL, Lang FF, Suki D, Sawaya RE. Extent of resection of glioblastoma revisited: personalized survival modeling facilitates more accurate survival prediction and supports a maximum-safe-resection approach to surgery. *J Clin Oncol*. 2014;32(8):774-782.
42. Qi S, Yu L, Li H, et al. Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms. *Oncol Lett*. 2014;7(6):1895-1902.
43. Wefel JS, Noll KR, Rao G, Cahill DP. Neurocognitive function varies by IDH1 genetic mutation status in patients with malignant glioma prior to surgical resection. *Neuro Oncol*. 2016;18(12):1656-1663.
44. Price SJ, Allinson K, Liu H, et al. Less invasive phenotype found in isocitrate dehydrogenase-mutated glioblastomas than in isocitrate dehydrogenase wild-type glioblastomas: a Diffusion-tensor imaging study. *Radiology*. 2017;283(1):215-221.
45. Kawaguchi T, Sonoda Y, Shibahara I, et al. Impact of gross total resection in patients with WHO grade III glioma harboring the IDH 1/2 mutation without the 1p/19q co-deletion. *J Neurooncol*. 2016;129(3):505-514.

46. Taylor JW, Chi AS, Cahill DP. Tailored therapy in diffuse gliomas: using molecular classifiers to optimize clinical management. *Oncology*. 2013;27(6):504-514.
47. Tan WL, Huang WY, Yin B, Xiong J, Wu JS, Geng DY. Can diffusion tensor imaging noninvasively detect IDH1 gene mutations in astrogliomas? A retrospective study of 112 cases. *AJNR Am J Neuroradiol*. 2014;35(5):920-927.
48. Kickingereder P, Sahm F, Radbruch A, et al. IDH mutation status is associated with a distinct hypoxia/angiogenesis transcriptome signature which is non-invasively predictable with rCBV imaging in human glioma. *Sci Rep*. 2015;5:16238. doi:10.1038/srep16238.
49. Yamashita K, Hiwatashi A, Togao O, et al. MR imaging-based analysis of glioblastoma multiforme: estimation of IDH1 mutation status. *AJNR Am J Neuroradiol*. 2016;37(1):58-65.
50. Andronesi OC, Kim GS, Gerstner E, et al. Detection of 2-hydroxyglutarate in IDH-mutated glioma patients by in vivo spectral-editing and 2D correlation magnetic resonance spectroscopy. *Sci Transl Med*. 2012;4(116):116ra114.
51. Pope WB, Prins RM, Albert Thomas M, et al. Non-invasive detection of 2-hydroxyglutarate and other metabolites in IDH1 mutant glioma patients using magnetic resonance spectroscopy. *J Neurooncol*. 2012;107(1):197-205.
52. Choi C, Ganji SK, DeBerardinis RJ, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. *Nat Med*. 2012;18(4):624-629.
53. Elkhaled A, Jalbert LE, Phillips JJ, et al. Magnetic resonance of 2-hydroxyglutarate in IDH1-mutated low-grade gliomas. *Sci Transl Med*. 2012;4(116):116ra115.
54. Lazovic J, Soto H, Piccioni D, et al. Detection of 2-hydroxyglutaric acid in vivo by proton magnetic resonance spectroscopy in U87 glioma cells overexpressing isocitrate dehydrogenase-1 mutation. *Neuro Oncol*. 2012;14(12):1465-1472.
55. Andronesi OC, Rapalino O, Gerstner E, et al. Detection of oncogenic IDH1 mutations using magnetic resonance spectroscopy of 2-hydroxyglutarate. *J Clin Invest*. 2013;123(9):3659-3663.
56. de la Fuente MI, Young RJ, Rubel J, et al. Integration of 2-hydroxyglutarate-proton magnetic resonance spectroscopy into clinical practice for disease monitoring in isocitrate dehydrogenase-mutant glioma. *Neuro Oncol*. 2016;18(2):283-290.
57. Emir UE, Larkin SJ, de Pennington N, et al. Noninvasive Quantification of 2-Hydroxyglutarate in Human Gliomas with IDH1 and IDH2 Mutations. *Cancer Res*. 2016;76(1):43-49.
58. Nagashima H, Tanaka K, Sasayama T, et al. Diagnostic value of glutamate with 2-hydroxyglutarate in magnetic resonance spectroscopy for IDH1 mutant glioma. *Neuro Oncol*. 2016;18(11):1559-1568.
59. Kanamori M, Kikuchi A, Watanabe M, et al. Rapid and sensitive intraoperative detection of mutations in the isocitrate dehydrogenase 1 and 2 genes during surgery for glioma. *J Neurosurg*. 2014;120(6):1288-1297.
60. Santagata S, Eberlin LS, Norton I, et al. Intraoperative mass spectrometry mapping of an onco-metabolite to guide brain tumor surgery. *Proc Natl Acad Sci USA*. 2014;111(30):11121-11126.
61. Shankar GM, Francis JM, Rinne ML, et al. Rapid intraoperative molecular characterization of glioma. *JAMA Oncol*. 2015;1(5):662-667.
62. Li S, Chou AP, Chen W, et al. Overexpression of isocitrate dehydrogenase mutant proteins renders glioma cells more sensitive to radiation. *Neuro Oncol*. 2013;15(1):57-68.
63. Wang XW, Labussiere M, Valable S, et al. IDH1(R132H) mutation increases U87 glioma cell sensitivity to radiation therapy in hypoxia. *Biomed Res Int*. 2014;2014:198697. doi:10.1155/2014/198697.
64. Kessler J, Guttler A, Wichmann H, et al. IDH1(R132H) mutation causes a less aggressive phenotype and radiosensitizes human malignant glioma cells independent of the oxygenation status. *Radiother Oncol*. 2015;116(3):381-387.
65. 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(4):487-494.
66. Koschmann C, Calinescu AA, Nunez FJ, et al. ATRX loss promotes tumor growth and impairs nonhomologous end joining DNA repair in glioma. *Sci Transl Med*. 2016;8(328):328ra328.
67. Baumert BG, Hegi ME, van den Bent MJ, et al. Temozolomide chemotherapy versus radiotherapy in high-risk low-grade glioma (EORTC 22033-26033): a randomised, open-label, phase 3 intergroup study. *Lancet Oncol*. 2016;17(11):1521-1532.
68. Andronesi OC, Loebel F, Bogner W, et al. Treatment response assessment in IDH-Mutant glioma patients by noninvasive 3D functional spectroscopic mapping of 2-Hydroxyglutarate. *Clin Cancer Res*. 2016;22(7):1632-1641.
69. Jafari-Khouzani K, Loebel F, Bogner W, et al. Volumetric relationship between 2-hydroxyglutarate and FLAIR hyperintensity has potential implications for radiotherapy planning of mutant IDH glioma patients. *Neuro Oncol*. 2016;18(11):1569-1578.