Oligodendroglial tumors: from biology to a better patient care

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Summary

Oligodendroglial tumors (pure oligodendrogliomas and oligoastrocytomas) are heterogenous in terms of molecular profile and outcome. Genetics has accomplished significant advances improving our knowledge and helping clinical management of oligodendroglioma patients: three prognostic subgroups are defined, in both grade II and grade III, based on the 1p19q codeletion and IDH1/2 mutation status: (i) 1p/19q codeleted (most of them are *CIC* mutated and all are *IDH1/IDH2* and *TERT* promoter mutated) which have the best outcome, (ii) non 1p19q co-deleted and *IDH* mutated (which have the *ATRX* mutation instead of *TERT* promoter mutation) with intermediate outcome and (iii) double negative with the poorest outcome. These subgroups have distinct natural history and the 1p19q codeletion is also associated with a better response to alkylating chemotherapy: recently, two trials (RTOG 9402 and EORTC 26951) have shown unambiguously near-doubling of median survival times (14.7 y *vs* 7.3 y in the RTOG study) of patients with 1p19q codeleted grade III gliomas treated with chemotherapy (PCV) and radiation therapy (RT) *vs* RT alone, whereas patient without codeletion have a poorer survival with marginal, no significant benefit of adjuvant chemotherapy. Based on these results, assessment of 1p/19q status is required in patients with grade III oligodendroglial tumor in order to deliver the right treatment. The recently identified molecular alterations (IDH1/2, CIC, FUBP1 and TERT promoter mutations) are attractive candidates to new molecular targeted agents, but further studies and better understanding are needed.

KEY WORDS: oligodendroglioma; IDH1; 1p19q codeletion; prognostic markers; adjuvant chemotherapy; PCV.

Introduction

WHO classification relies on similarities between tumor cells and normal glial cells to identify astrocytomas, oligodendrogliomas, and mixed oligoastrocytomas. It is highly subjective and poorly reproducible, leading a high inter-observer variability (1). The importance of correct identification of oligodendroglioma in clinical practice was raised twenty years ago with the observation that some oligodendrogliomas, unlike common astrocytic gliomas, were particularly sensitive to chemotherapy (2). The chemosensitivity has been then associated to the presence of the combined loss of chromosomes 1p and 19q (3). Based on the CBTRUS studies, oligodendrogliomas account for approximately 2% of all primary brain tumors and 6% of gliomas (4). In other series, oligodendrogliomas represent up to 20% of all gliomas. Oligodendroglioma is characterized by monomorphic cells with uniform round nuclei and perinuclear halos with honeycomb appearance. In addition significant mitotic activity, prominent microvascular proliferation or necrosis defines anaplastic oligodendroglioma (5). In clinical practice the diagnosis of oligodendroglioma remains challenging. The clinical behavior of oligodendroglioma is heterogeneous within the same pathological WHO grade, and particularly in grade III, and this is in part explained by the molecular profile.
Indeed, over the last years, major efforts have been accomplished to discover the genes driving oligodendroglial oncogenesis and to identify relevant biomarkers for clinical use. The first milestone in genetics of oligodendrogliomas was the detection of recurrent co-deletion of chromosome regions 1p and 19q. This chromosome imbalance, observed in ~2/3 of pure oligodendrogliomas and 10-15% of mixed oligoastrocytomas, is associated with better outcome and better response to chemotherapy and should now be part of the pre therapeutic screening. More recently, pivotal studies using high throughput molecular biology technics have identified novel mutated genes with clinical and biological perspectives.

Chromosome arms 1p/19q co-deletion is a prognostic and predictive marker

In the nineties, microsatellites analysis identified recurrent losses of heterozygosity (LOH) in chromosome regions 1p36 and 19q13 (6). This signature was associated with

frontal location and classic oligodendroglial morphology (7). Early retrospective studies suggested that this codeletion of chromosome 1p and 19q, was the response to chemotherapy and longer progression-free survival in anaplastic oligodendrogliomas (3). It was then shown in low grade gliomas that 1p19q codeletion has a different natural history with slower growth rate (8). In fact until recently, it was still unclear whether 1p19q loss was predictive for chemotherapy or merely indicates a different natural history: two trials from the Radiation Therapy Oncology Group (RTOG 9402) and European Organisation for Research and Treatment (EORTC 26951) shows clearly near-doubling of median survival times (14.7y vs 7.3y in the RTOG study) of patients with 1p19q codeleted grade III gliomas treated with chemotherapy and radiation therapy (RT) *vs* RT alone, whereas patient without codeletion have a poor survival (2.6-2.7 y) and no significant benefit of adjuvant chemotherapy (9, 10).
The identification of the 1p19q codeletion is therefore critical for the clinician, but may be challenging and requires an adequate technique. Indeed the "true" 1p19q codeletion [i.e. with centromeric breackpoint, as identified by comparative genomic hybridization (CGHa)] must be distinguished from partial deletions of 1p which can be associated with 19q loss and are associated with poorer outcome (11). The 1p19q codeleted gliomas over express proneural genes (12): one of them is INA which encodes alpha-internexin (INA), a class IV neuronal intermediate filament. Immunohistochemical INA analysis can be used routinely, is useful to predict 1p19q codeletion and is a simple and valuable prognostic and predictive factor for adjuvant chemotherapy (13,14). INA expression was found to be a strong pronostic factor in patients with anaplastic oligodendroglial tumors enrolled in the EORTC trial 26951 (15).
This 1p19q co-deletion with centromeric breakpoints (11) was highly suggestive of an imbalanced reciprocal translocation, t (1; 19) (q10; p10), that has been proven by fluorescent *in situ* hybridization (FISH) analysis (16). No chimeric gene created by this chromosome fusion has been identified to date (17). In addition these cells are extremely difficult to grow in culture (18), and therefore relevant experimental models are missing.

The other genomic copy number abnormalities are associated with poor outcome

EGFR amplification and chromosome arm 21q deletion are mutually exclusive with 1p19q codeletion and predictive of poor prognosis. *EGFR* amplification is associated with high rate of necrosis, older age of patients (19). In grade II and III oligodendrogliomas chromosome arm 10q loss is predictive of poor prognosis in terms of both progression free and overall survival (20), and in the same line, the looses of chromosome arms 9p and 10q have been associated with poor outcome in WHO grade II oligodendrogliomas, irrespective of 1p/19q status (21).

Recurrent gene mutations

Over the recent last years, next generation sequencing technologies identified novel mutated genes in gliomas, and particularly in oligodendrogliomas with 1p19q codeletion.

IDH mutations are a constant feature in 1p19q codeleted oligodendrogliomas

The *IDH1* mutation has been identified by high throughput sequencing of glioblastoma (22). In fact *IDH1* mutation, which affect 40% of gliomas, is found in only 5-8% of primary glioblastoma, vs 75% of grade II and 50% of grade III gliomas (23). *IDH1* encodes the cytoplasmic isoform of isocitrate dehydrogenase. Mutation affects the residue 132 of the *IDH1* gene, the majority (>90%) being a CGT→CAT change, leading to an Arg^{132}→His substitution. Some patients without *IDH1* mutations harbor a mutation in the analogous amino acid residue (Arg^{172}) of the mitochondrial isoform *IDH2* (24). Strikingly *IDH1/IDH2* mutations are tightly associated with genetic profile, and are a constant feature in 1p19q codeleted gliomas (25), suggesting a potential link between both alterations. *IDH1* R132H detection is now considerably facilitated by the development of two monoclonal antibodies specifically targeted against the *IDH1* R132H mutation (26, 27).
IDH1/IDH2 mutated tumors have a better outcome, whatever grade considered (23, 28, 29). Whether *IDH1/IDH2* mutation can predict response to treatment in gliomas needs to be further investigated (30).
The mutation causes the loss of the isocitrate dehydrogenase function and the gain of an α-ketoglutarate reductase function leading to the cellular accumulation of D-2-hydroxyglutarate (D-2HG) (31). The rate of D-2HG in *IDH* mutated tumors is increased by a factor >100, thus representing a diagnostic marker (this change is almost specific for gliomas) and prognostic (mutated gliomas have longer survival) of interest. Interestingly, D-2HG can be detected using proton magnetic resonance spectroscopy (MRS) (32, 33).
The accumulation of D-2HG results in a profound modulation of epigenome (genomic DNA methylation resulting in CIMP= CpG Island Methylated Phenotype and histone methylation), gene expression and inhibition of terminal differentiation (34, 35). As a consequence of diffuse CpG methylation, IDH1/2 mutated tumors, including all the 1p19q codeleted oligodendrogliomas, are tightly associated with methylation of *MGMT* promoter (and consequently gene silencing) (35, 36). *MGMT* gene encodes the Methyl-Guanyl-Methyl-Transferase enzyme which removes the methyl from the O6 residue of guanine and is therefore involved in the chemoresistance to alkylant agents, such as temozolomide or nitrosoureas. In the same line, a genome-wide methylation profiling study of oligodendroglial WHO grade III tumors from the EORTC study 26951 clinical trial, showed that: (i) CpG island hypermethylation phenotype (CIMP+) is associated with *MGMT* promoter methylation, 1p/19q codeletion, *IDH* mutation and (ii) CIMP+ tumors have better prognosis than CIMP- and (iii) CIMP+ is an independent prognostic factor in multivariate analysis. CIMP+ and *IDH* mutation correlation is in agreement with the functional link mentioned above (36). In anaplastic oligodendrogliomas, MGMT promoter methylation seems to be a part of the broader CIMP+, that explain that MGMT methylated tumors, whatever their treatment, have a better outcome. Similarly, recent studies have demonstrated that IDH mutated glioma have singular proteomic and metabolomics patterns (37, 38).

CIC and FUBP1 mutations in oligodendrogliomas

Using high throughput sequencing, recurrent mutations of *CIC* (homologue of capicua Drosophila) and *FUBP1* (Far Upstream Element Binding Protein 1) have been identified in 1p/19q co-deleted oligodendrogliomas.
CIC map to chromosome region 19q13.2 and encodes a DNA binding high mobility group (HMG)-box transcriptional repressor downstream of the receptor tyrosine kinase (RTK)-Ras-MAPK signaling pathways. It is mutated in the majority (70%) of 1p/19q co-deleted but very rarely in non 1p19q co-deleted oligodendrogliomas (39-41).
FUBP1, located on chromosome region 1p31.1, encodes a DNA helicase acting as a dual (i.e. activator or inhibitor) transcriptional modulator of C-MYC oncogene expression. *FUBP1* mutations are also restricted to 1p/19q co-deleted oligodendrogliomas (39, 41).

TERT mutations in oligodendrogliomas

Very recently mutations involving *TERT* promoter (C228T and C250T, corresponding to the positions 124 and 146 bp upstream of the *TERT* ATG start site) have been reported in gliomas, involving 80% of glioblastoma and 100% of oligodendrogliomas with 1p19q codeletion (42). TERT encodes the telomerase reverse transcriptase involved in the maintenance of telomere length. In the absence of telomerase activity, telomeres shorten with each cell division. Unlimited cancer cells division requires some telomere maintenance mechanism to avoid cell death or senescence. It is particularly interesting to note that *TERT* mutation were mutually exclusive with gliomas with *ATRX* mutation: *ATRX* inactivation is involved in another alternative mechanism of telomere lenghtening (ALT).

Molecular classification of oligodendrogliomas has a prognostic impact

We can define three subgroups of oligodendrogliomas/oligoastrocytomas, based on the genetic profile: (i) 1p/19q codeleted (most of them are *CIC* mutated and all are *IDH* and *TERT* promoter mutated), (ii) non 1p19q co-deleted and *IDH* mutated (which have the *ATRX* mutation instead of *TERT* promoter mutation) and (iii) double negative. These subgroups have distinct molecular patterns (epigenetic, transcriptomic, proteomic and metabolomics), distinct natural history and response to alkylating chemotherapy.
Oligodendrogliomas with 1p/19q co-deletion and *IDH* mutation (group 1) are characterized by better prognosis and better response to chemotherapy. They are associated with cerebral frontal location, classic morphology, absence of gene high-level amplification. Recently, it has validated through phase III clinical trials that 1p/19q status is critical for medical management of anaplastic oligodendroglioma patients (see below). The interactions between the key genetic alterations of this tumor subgroup (particularly 1p/19q codeletion, *IDH* mutation, *CIC* mutation, and TERT promoter mutation) need to be elucidated particularly in oligodendrocyte progenitor that been recently suggested as the cell of origin of oligodendroglioma. Novel sequencing technologies such as RNA-Seq and development of tumor cell lines and animal models harboring this abnormality will probably be helpful to dissect molecular oncogenesis of 1p/19q co-deleted oligodendrogliomas.
IDH mutated gliomas without 1p/19q codeletion (group 2), have an intermediate prognosis (poorer than 1p19q codeleted, but better than the non *IDH* mutated counterparts) (25), and include mostly astrocytomas, and occasionaly oligodendrogliomas and oligoastrocytomas. Mutation of *P53* and *ATRX* are frequent (43). ATRX is part of a chromatin remodeling complex involved in telomere biology. Mutations of *ATRX* cause alternative lengthening of telomeres (ALT) and are mutually exclusive with *TERT* promoter mutations (42).
IDH wild type gliomas (and consequently non 1p/19q codeleted- group 3) have poor prognosis and are mostly represented by mixed oligoastrocytomas. In grade II, group 3 is nearly similar to the “triple negative” recently identified subgroup of low grade glioma characterized by absence of 1p/19q codeletion, TP53 expression and IDH mutation (44) (1p19q deletion is virtually absent in 1p19q, and TP53 expression, mostly found in *IDH* mutated-non codeleted tumors, is infrequent in *IDH* wild-type tumors). Most of these LGG have oligodendroglial or mixed phenotype. In addition, they are frequently located in the insula, larger in size and associated with poor prognosis. These triple negative WHO grade II tumors have probably distinct oncogenic mechanism compared to the majority of oligodendrogliomas exhibiting *IDH* mutation (45).

Radiological correlations

Several evidences suggest that human oligodendroglioma have a white matter origin, and derive from OPCs (Oligodendrocytes Progenitor Cells) rather than Neural stem Cells (46). Tumors with intact 1p/19q are more frequent in the temporoinsular regions whereas 1p/19q codeleted tumors are more frequently located in the frontal lobe (7). Low grade oligodendroglioma with 1p/19q codeletion have higher regional cerebral blood volume (rCBV) and blood flow (rCBF) but a lower apparent diffusion coefficient (ADC) than their non codeleted counterparts (47, 48). Quantitative MR texture may also help to differenciate 1p19q codeleted and non codeleted tumors (49). However, the most promising approach today is the possibility to detect the D-2HG produced by IDH mutated tumors by spectro-MRI (32, 33). In the near future this feature may be useful for non-invasive diagnosis of *IDH* mutated gliomas and oligodendrogliomas.

Therapeutic option in oligodendroglial tumors

The optimal treatment strategy for anaplastic oligodendroglioma tumor is evolving.
Low grade oligodendroglial tumors are slow-growing tumors, and share with astrocytic and mixed LGG invasive and malignant potential. Gross total surgical resection, whenever possible, is recommended. Radiotherapy is considered as a postoperative standard treatment for LGG, but the optimal timing of this treatment (i.e., immediate vs at progression) is still discussed. There are now consistent evidences suggesting that up-front chemotherapy, with temozolomide or PCV regimen, is a valuable alternative to radiotherapy, in non resectable and sympto-

matic LGG (50, 51). Moreover, the 1p19q codeleted oligodendrogliomas have a slower growing rate, a higher response rate to chemotherapy, and more sustained response (8,51). The recently completed EORTC 22033-26033 trial that randomises at progression temozolomide *vs* radiotherapy in patients with low grade gliomas will help to determine the best option, according to the genomic profile (ie 1p19q codeletion, *IDH* mutation).
The treatment of anaplastic gliomas is based on post-operative radiotherapy. The EORTC Brain Tumor Group initiated in 1995 a prospective randomized phase III trial (EORTC study 26951) to determine whether adjuvant PCV given after 59.4 Gy of radiotherapy (RT) in fractions of 1.8 Gy would improve survival.
After a median follow-up of 7 years, the results showed an increase in progression-free survival (PFS) in adjuvant PCV-treated patients, but no statistically significant increase in overall survival (OS), whatever the molecular profile (52). A similar North American study (RTOG 9402) in which PCV chemotherapy was given with an intensified PCV regimen before 59.4 Gy of RT reached similar conclusions (53). In both studies median OS was not reached for the 1p/19q codeletion.
However six years later updated analysis with a median follow-up of 12 years demonstrated that patients with codeleted 1p19q grade III oligodendrogliomas, had a significant improvement in overall survival when treated with early chemotherapy with radiation compared with early radiation, and salvage chemotherapy at tumor relapse, and thus establishes the 1p19q codeletion as a predictive marker (9, 10). Radiotherapy alone should no longer be considered an adequate treatment for this patient population. However, there are still unanswered questions regarding the quality of life of this long term survivor category: should upfront chemotherapy, omitting/deferring radiotherapy, be the initial therapy for oligodendroglial tumors with codeleted 1p19q, in order to avoid late neurocognitive toxicity? Can temozolomide, an oral agent with a better toxicity profile, be substituted for PCV? Indeed randomized German trial (NOA-04) suggested that upfront radiotherapy or chemotherapy (with either temozolomide or PCV) achieved comparable results in patients with anaplastic gliomas (29).
In cases without 1p19q deletion (group 2 and 3), most neuro-oncologists still associate chemotherapy to radiotherapy into the upfront strategy: 1) in group 2 the RTOG 9402 data suggest a benefit of upfront PCV in *IDH* mutated, non codeleted anaplastic oligodendrogliomas, and 2) several neuro-oncologists treat the non mutated *IDH* grade III tumors (group 3) with concomitant and adjuvant temozolomide, considering their survival range similar to true glioblastomas. This question will be in fact answered by the ongoing EORTC 26053-22054 (CATNON) that evaluates the benefit of concomitant and/or adjuvant chemotherapy to fractionated radiotherapy in grade III non 1p19q codeleted gliomas, stratified according to MGMT promoter methylation and *IDH1* mutated status.
The molecular profiling has revolutionized histo-molecular classification of oligodendroglial tumors, and identified at least three distinct prognostic profiles. Secondly, 1p19q codeletion in anaplastic grade III oligodendrogliomas and mixed oligoastrocytomas should be now considered not only as a prognostic but, most importantly, predictive factor of response to adjuvant PCV chemotherapy. Based on these results, medical management of patients with anaplastic gliomas has changed and requires now assessment of 1p/19q status to deliver the right treatment to 1p/19q codeleted anaplastic oligodendrogliomas patients (i.e. radiotherapy plus PCV). The parternship between *IDH, CIC, FUBP1* and *TERT* mutations and 1p/19q co-deletion in oligodendroglioma genesis remains to be elucidated. These molecular alterations might be candidates to new molecular targeted agents. Further studies are warranted and the increasing understanding of molecular pathways involved may lead to more selective therapeutic targets in the future.

References

1. Coons SW JP, Scheithauer BW, Yates AJ, Pearl DK. Improving diagnostic accuracy and interobserver concordance in the classification and grading of primary gliomas. Cancer 1997; 79:1381-1393.
2. Cairncross JG, Macdonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. Ann Neurol 1988, 23:360-364.
3. Cairncross JG, Ueki K, Zlatescu MC, Lisle DK, Finkelstein DM, Hammond RR, Silver JS, Stark PC, Macdonald DR, Ino Y, et al.: Specific genetic predictors of chemotherapeutic response and survival in patients with anaplastic oligodendrogliomas. J Natl Cancer Inst 1998; 90:1473-1479.
4. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol 2012; 14 Suppl 5:v1-49.
5. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, Scheithauer BW, Kleihues P. The 2007 WHO classification of tumours of the central nervous system. Acta Neuropathol 2007; 114:97-109.
6. Reifenberger J, Reifenberger G, Liu L, James CD, Wechsler W, Collins VP. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol 1994; 145:1175-1190.
7. Laigle-Donadey F, Martin-Duverneuil N, Lejeune J, Criniere E, Capelle L, Duffau H, Cornu P, Broet P, Kujas M, Mokhtari K, et al. Correlations between molecular profile and radiologic pattern in oligodendroglial tumors. Neurology 2004; 63:2360-2362.
8. Ricard D, Kaloshi G, Amiel-Benouaich A, Lejeune J, Marie Y, Mandonnet E, Kujas M, Mokhtari K, Taillibert S, Laigle-Donadey F, et al. Dynamic history of low-grade gliomas before and after temozolomide treatment. Ann Neurol 2007; 61:484-490.
9. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, Fink K, Souhami L, Laperriere N, Curran W, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 2013; 31:337-343.
10. van den Bent MJ, Brandes AA, Taphoorn MJ, Kros JM, Kouwenhoven MC, Delattre JY, Bernsen HJ, Frenay M, Tijssen CC, Grisold W, 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.

11. Idbaih A, Marie Y, Pierron G, Brennetot C, Hoang-Xuan K, Kujas M, Mokhtari K, Sanson M, Lejeune J, Aurias A, et al. Two types of chromosome 1p losses with opposite significance in gliomas. Ann Neurol 2005; 58:483-487.
12. Ducray F, Idbaih A, de Reynies A, Bieche I, Thillet J, Mokhtari K, Lair S, Marie Y, Paris S, Vidaud M, et al. Anaplastic oligodendrogliomas with 1p19q codeletion have a proneural gene expression profile. Mol Cancer 2008; 7:41.
13. Ducray F, Criniere E, Idbaih A, Mokhtari K, Marie Y, Paris S, Navarro S, Laigle-Donadey F, Dehais C, Thillet J, et al. alpha-Internexin expression identifies 1p19q codeleted gliomas. Neurology 2009; 72:156-161.
14. Ducray F, Mokhtari K, Criniere E, Idbaih A, Marie Y, Dehais C, Paris S, Carpentier C, Dieme MJ, Adam C, et al. Diagnostic and prognostic value of alpha internexin expression in a series of 409 gliomas. Eur J Cancer 2011; 47:802-808.
15. Mokhtari K, Ducray F, Kros JM, Gorlia T, Idbaih A, Taphoorn M, Wesseling P, Hoang-Xuan K, Van den Bent M, Sanson M. Alpha-internexin expression predicts outcome in anaplastic oligodendroglial tumors and may positively impact the efficacy of chemotherapy: European organization for research and treatment of cancer trial 26951. Cancer 2011; 117:3014-3026.
16. Jenkins RB, Blair H, Ballman KV, Giannini C, Arusell RM, Law M, Flynn H, Passe S, Felten S, Brown PD, et al. A t(1;19)(q10;p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer Res 2006; 66:9852-9861.
17. Benetkiewicz M, Idbaih A, Cousin PY, Boisselier B, Marie Y, Criniere E, Hoang-Xuan K, Delattre JY, Sanson M, Delattre O. NOTCH2 is neither rearranged nor mutated in t(1;19) positive oligodendrogliomas. PLoS One 2009; 4:e4107.
18. Kelly JJ, Blough MD, Stechishin OD, Chan JA, Beauchamp D, Perizzolo M, Demetrick DJ, Steele L, Auer RN, Hader WJ, et al. Oligodendroglioma cell lines containing t(1;19)(q10;p10). Neuro Oncol 2010; 12:745-755.
19. Idbaih A, Dalmasso C, Kouwenhoven M, Jeuken J, Carpentier C, Gorlia T, Kros JM, French P, Teepen J, Broet P, et al. Genomic aberrations associated with outcome in anaplastic oligodendroglial tumors treated within the EORTC phase III trial 26951. J Neurooncol 2011; 103:221-230.
20. Ramirez C, Bowman C, Maurage CA, Dubois F, Blond S, Porchet N, Escande F. Loss of 1p, 19q, and 10q heterozygosity prospectively predicts prognosis of oligodendroglial tumors-towards individualized tumor treatment? Neuro Oncol 2010; 12:490-499.
21. Houillier C, Mokhtari K, Carpentier C, Criniere E, Marie Y, Rousseau A, Kaloshi G, Dehais C, Laffaire J, Laigle-Donadey F, et al. Chromosome 9p and 10q losses predict unfavorable outcome in low-grade gliomas. Neuro Oncol 2010; 12:2-6.
22. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, et al. An integrated genomic analysis of human glioblastoma multiforme. Science 2008; 321:1807-1812.
23. Sanson M, Marie Y, Paris S, Idbaih A, Laffaire J, Ducray F, El Hallani S, Boisselier B, Mokhtari K, Hoang-Xuan K, et al. Isocitrate dehydrogenase 1 codon 132 mutation is an important prognostic biomarker in gliomas. J Clin Oncol 2009; 27:4150-4154.
24. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W, Kos I, Batinic-Haberle I, Jones S, Riggins GJ, et al. IDH1 and IDH2 Mutations in Gliomas. N Engl J Med 2009; 360:765-773.
25. Labussiere M, Idbaih A, Wang XW, Marie Y, Boisselier B, Falet C, Paris S, Laffaire J, Carpentier C, Criniere E, et al. All the 1p19q codeleted gliomas are mutated on IDH1 or IDH2. Neurology 2010; 74:1886-1890.
26. Capper D, Weissert S, Balss J, Habel A, Meyer J, Jager D, Ackermann U, Tessmer C, Korshunov A, Zentgraf H, et al. Characterization of R132H Mutation-specific IDH1 Antibody Binding in Brain Tumors. Brain Pathol 2010; 20:245-254.
27. Kato Y, Jin G, Kuan CT, McLendon RE, Yan H, Bigner DD. A monoclonal antibody IMab-1 specifically recognizes IDH1R132H, the most common glioma-derived mutation. Biochem Biophys Res Commun 2009; 390:547-551.
28. Nobusawa S, Watanabe T, Kleihues P, Ohgaki H. IDH1 mutations as molecular signature and predictive factor of secondary glioblastomas. Clin Cancer Res 2009; 15:6002-6007.
29. Wick W, Hartmann C, Engel C, Stoffels M, Felsberg J, Stockhammer F, Sabel MC, Koeppen S, Ketter R, Meyermann R, 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; 27:5874-5880.
30. van den Bent MJ, Dubbink HJ, Marie Y, Brandes AA, Taphoorn MJ, Wesseling P, Frenay M, Tijssen CC, Lacombe D, Idbaih A, et al. IDH1 and IDH2 Mutations Are Prognostic but not Predictive for Outcome in Anaplastic Oligodendroglial Tumors: A Report of the European Organization for Research and Treatment of Cancer Brain Tumor Group. Clin Cancer Res 2010; 16:1597-1604.
31. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009; 462:739-744.
32. Choi C, Ganji SK, Deberardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, Yang XL, Mashimo T, Raisanen JM, Marin-Valencia I, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012; 18:624-629.
33. Andronesi OC, Kim GS, Gerstner E, Batchelor T, Tzika AA, Fantin VR, Vander Heiden MG, Sorensen AG. Detection of 2-Hydroxyglutarate in IDH-Mutated Glioma Patients by In Vivo Spectral-Editing and 2D Correlation Magnetic Resonance Spectroscopy. Science Translational Medicine 2012; 4:116ra114.
34. Lu C, Ward PS, Kapoor GS, Rohle D, Turcan S, Abdel-Wahab O, Edwards CR, Khanin R, Figueroa ME, Melnick A, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature 2012; 483:474-478.
35. Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, Campos C, Fabius AW, Lu C, Ward PS, et al.

IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature 2012; 483:479-483.
36. van den Bent MJ, Gravendeel LA, Gorlia T, Kros JM, Lapre L, Wesseling P, Teepen JL, Idbaih A, Sanson M, Smitt PA, et al. A hypermethylated phenotype is a better predictor of survival than MGMT methylation in anaplastic oligodendroglial brain tumors: a report from EORTC study 26951. Clin Cancer Res 2011; 17:7148-7155.
37. Thirant C, Varlet P, Lipecka J, Le Gall M, Broussard C, Chafey P, Studler JM, Lacombe J, Lions S, Guillaudeau A, et al. Proteomic analysis of oligodendrogliomas expressing a mutant isocitrate dehydrogenase-1. Proteomics 2011; 11:4139-4154.
38. Reitman ZJ, Jin G, Karoly ED, Spasojevic I, Yang J, Kinzler KW, He Y, Bigner DD, Vogelstein B, Yan H. Profiling the effects of isocitrate dehydrogenase 1 and 2 mutations on the cellular metabolome. Proc Natl Acad Sci U S A 2011; 108:3270-3275.
39. Bettegowda C, Agrawal N, Jiao Y, Sausen M, Wood LD, Hruban RH, Rodriguez FJ, Cahill DP, McLendon R, Riggins G, et al. Mutations in CIC and FUBP1 contribute to human oligodendroglioma. Science 2011; 333:1453-1455.
40. Yip S, Butterfield YS, Morozova O, Chittaranjan S, Blough MD, An J, Birol I, Chesnelong C, Chiu R, Chuah E, et al. Concurrent CIC mutations, IDH mutations, and 1p/19q loss distinguish oligodendrogliomas from other cancers. J Pathol 2012; 226:7-16.
41. Sahm F, Koelsche C, Meyer J, Pusch S, Lindenberg K, Mueller W, Herold-Mende C, von Deimling A, Hartmann C. CIC and FUBP1 mutations in oligodendrogliomas, oligoastrocytomas and astrocytomas. Acta Neuropathol 2012; 123:853-860.
42. Killela PJ, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA, Jr., Friedman AH, Friedman H, Gallia GL, Giovanella BC, 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 U S A 2013.
43. Liu XY, Gerges N, Korshunov A, Sabha N, Khuong-Quang DA, Fontebasso AM, Fleming A, Hadjadj D, Schwartzentruber J, Majewski J, et al. Frequent ATRX mutations and loss of expression in adult diffuse astrocytic tumors carrying IDH1/IDH2 and TP53 mutations. Acta Neuropathol 2012; 124:615-625.
44. Metellus P, Coulibaly B, Colin C, de Paula AM, Vasiljevic A, Taieb D, Barlier A, Boisselier B, Mokhtari K, Wang XW, et al. Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis. Acta Neuropathol 2011; 120:719-729.
45. Kim YH, Nobusawa S, Mittelbronn M, Paulus W, Brokinkel B, Keyvani K, Sure U, Wrede K, Nakazato Y, Tanaka Y, et al. Molecular classification of low-grade diffuse gliomas. Am J Pathol 2010; 177:2708-2714.
46. Persson AI, Petritsch C, Swartling FJ, Itsara M, Sim FJ, Auvergne R, Goldenberg DD, Vandenberg SR, Nguyen KN, Yakovenko S, et al. Non-stem cell origin for oligodendroglioma. Cancer Cell 2010; 18:669-682.
47. Fellah S, Caudal D, De Paula AM, Dory-Lautrec P, Figarella-Branger D, Chinot O, Metellus P, Cozzone PJ, Confort-Gouny S, Ghattas B, et al. Multimodal MR Imaging (Diffusion, Perfusion, and Spectroscopy): Is It Possible To Distinguish Oligodendroglial Tumor Grade and 1p/19q Codeletion in the Pretherapeutic Diagnosis? AJNR Am J Neuroradiol 2012.
48. Khayal IS, VandenBerg SR, Smith KJ, Cloyd CP, Chang SM, Cha S, Nelson SJ, McKnight TR. MRI apparent diffusion coefficient reflects histopathologic subtype, axonal disruption, and tumor fraction in diffuse-type grade II gliomas. Neuro-Oncology 2011, 13:1192-1201.
49. Brown R, Zlatescu M, Sijben A, Roldan G, Easaw J, Forsyth P, Parney I, Sevick R, Yan E, Demetrick D, et al. The use of magnetic resonance imaging to noninvasively detect genetic signatures in oligodendroglioma. Clin Cancer Res 2008; 14:2357-2362.
50. Hoang-Xuan K CL, Kujas M, Taillibert S, Duffau H, Lejeune J, Polivka M, Criniere E, Marie Y, Mokhtari K, Carpentier AF, Laigle F, Simon JM, Cornu P, Broet P, Sanson M, Delattre JY. Temozolomide as initial treatment for adults with low-grade oligodendrogliomas or oligoastrocytomas and correlation with chromosome 1p deletions. J Clin Oncol 2004; 22:3133-3138.
51. Kaloshi G, Benouaich-Amiel A, Diakite F, Taillibert S, Lejeune J, Laigle-Donadey F, Renard MA, Iraqi W, Idbaih A, Paris S, et al. Temozolomide for low-grade gliomas: predictive impact of 1p/19q loss on response and outcome. Neurology 2007; 68:1831-1836.
52. van den Bent MJ, Carpentier AF, Brandes AA, Sanson M, Taphoorn MJ, Bernsen HJ, Frenay M, Tijssen CC, Grisold W, Sipos L, et al. Adjuvant procarbazine, lomustine, and vincristine improves progression-free survival but not overall survival in newly diagnosed anaplastic oligodendrogliomas and oligoastrocytomas: a randomized European Organisation for Research and Treatment of Cancer phase III trial. J Clin Oncol 2006; 24:2715-2722.
53. Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, Buckner J, Fink K, Souhami L, Laperierre N, 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; 24:2707-2714.