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REVIEW ARTICLE

Overcoming the Odds: Toward a Molecular Profile of Long-Term Survival in Glioblastoma

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Abstract

For over a century, gliomas were characterized solely by histologic features. With the publication of the *WHO Classification of Tumours of the Central Nervous System, Revised 4th Edition* in 2016, integrated histologic and molecular diagnosis became the norm, providing improved tumor grading and prognosis with *IDH1/2* (isocitrate dehydrogenase 1 and 2) mutation being the most significant prognostic feature in all grades of adult diffuse glioma. Since then, much work has been done to identify additional molecular prognostic features, but the bulk of the progress has been made in defining aggressive features in lower grade astrocytoma. Although there have been several large case series of glioblastomas with long-term survival (LTS; overall survival $\geq$36 months), less is known about the clinical and molecular features of these cases. Herein, we review 19 studies examining LTS glioblastoma patients from 2009 to 2020 that include variable molecular analysis, including 465 cases with survival of 36 months or more (total n = 2328). These studies suggest that while there is no definitive molecular signature of long survival, younger age, IDH mutation, and *MGMT* (methyl guanine methyl transferase) promoter hypermethylation are associated with longer overall survival, and in IDH-wildtype tumors, chromosome 19/20 co-gain and lack of *EGFR* amplification, chromosome 7 gain/10 loss, and *TERT* promoter mutation are associated with LTS.

Key Words: 7+/10-, 19+/20+, CCND2, EGFR, IDH mutation, MGMT, *TERT*.

INTRODUCTION

Diffuse infiltrating gliomas are the second most common group of intracranial neoplasms in adults (~25% of all tumors). The most aggressive tumor in this class, glioblastoma (GBM; WHO grade IV) is the most common diffuse glial neoplasm, comprising ~48% of all malignant CNS tumors and 15% of total intracranial neoplasms with almost 12 000 cases reported annually in the United States (1). Historically, GBM has been classified based exclusively on histologic features, with "astrocytic morphology," infiltration as single cells, mitotic activity, microvascular proliferation, and necrosis being characteristics features (2). In recent decades, work by numerous groups has made it clear that gliomas in general and GBMs in particular form a heterogeneous group of entities distinguishable by distinct molecular features, some of which hold prognostic significance (3).

As a result of these efforts, the *WHO Classification of Tumours of the Central Nervous System, Revised 4th Edition* categorized diffuse glial neoplasms with combined histologic-molecular diagnoses (3), and isocitrate dehydrogenase 1 and 2 (*IDH1/2*) mutation was recognized as the most important prognostic factor in astrocytoma, as patients with grades II–IV all survived significantly longer than their grade-matched IDH-wildtype counterparts (3–6). Since the publication of the updated WHO classification system in 2016, numerous other studies have sought additional prognostic factors beyond IDH1/2 to further refine prognostic categories and account for survival outliers (7). However, these studies have focused primarily on molecular features of lower grade astrocytomas, identifying numerous potential clinically useful adverse prognostic factors in these subgroups (8–21), with less emphasis on beneficial molecular factors in histologic GBMs.

When compared with IDH-wildtype GBM, IDH-mutant GBM forms the minority of new GBM diagnoses (<10% of total GBM cases), occurs in younger individuals (median age at diagnosis of 45 years old compared with 62 years old in IDH wildtype), and has longer median survival intervals after surgery (24–31 months compared with 10–15 months) (3). Even with recent advances in treatment, the overall expected 5-year survival rate is <5% for all GBMs, and "long survival" is defined by most modern studies as $\geq$36 months postsurgery (22–26). Although case reports and case series of longer

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survival in patients diagnosed with GBM exist in the literature with examples dating back to the mid20th century (27, 28), there remains a need to identify potential clinical, radiologic, and molecular features to refine GBM diagnosis and prognosis beyond separating cases into *IDH1/2*-wildtype and -mutant categories.

In this review, we identified 19 studies of 2328 histologic GBMs, including 465 with survival longer than 36 months (Table 1). Most of the studies included here derive focal molecular information from targeted panels performed on institutional cohorts instead of comprehensive genetic platforms to identify all potential mutations, copy number alterations, and methylation profile abnormalities, and as such this remains an incomplete picture. More work is needed to comprehensively profile GBM cases with long-term survival (LTS) and compare those to short-term survival (STS) cases to truly define reliable prognostic molecular features in large-scale studies such as The Cancer Genome Atlas (TCGA; 10, 11, 22). Although there is not yet a definitive molecular signature to identify cases with longer survival in the GBM category, multiple features exist in GBM generally and within IDH-wildtype and -mutant groups more specifically that may help guide clinical decision making and may give clues to the underlying tumor biology that makes the vast majority of GBM cases extremely aggressive.

MATERIALS AND METHODS

A search of the English literature using PubMed, Google Scholar, and Scopus databases was performed focusing on studies published between 2005 and 2020, and searching for "glioblastoma," "GBM," "LTS," "STS," "36 months," "molecular," "genetic," and "methylation." GBM was defined by histologic criteria according to the 2016 *WHO Classification of Tumours of the Central Nervous System, Revised 4th Edition*. All relevant studies with survival data and molecular data were examined and, where possible, paired survival and molecular data were retrieved from tables and supplementary materials for further statistical analysis. Multivariate analysis was performed where possible; however, many of the studies included do not have comprehensive molecular profiling, precluding full multivariate analysis of some molecular variables. Survival analysis was performed using Log-rank (Mantel–Cox) test. The Fisher exact test was used to compare the frequency of individual alterations between groups. All statistical analysis was performed with GraphPad Prism version 8 (GraphPad, La Jolla, CA).

O-6-METHYLGUANINE-DNA METHYLTRANSFERASE PROMOTER METHYLATION

The most frequently considered molecular feature in the studies evaluated in this review was *O-6-methylguanine methyl transferase* (*MGMT*) promoter hypermethylation, with 17 studies including reliable information on *MGMT* status (25, 29–44). MGMT is a DNA repair protein that when active confers protection against alkylating chemotherapeutic agents in tumor cells; *MGMT* promoter hypermethylation is correlated to decreased MGMT protein and has been identified as a positive predictive factor for response to temozolomide therapy (45–47).

MGMT promoter hypermethylation was found to be more frequent in LTS cases compared with those with shorter overall survival (OS) in both IDH-mutant and -wildtype GBMs in the majority of studies (Table 1), although this was not true of all included studies (39, 44). In previous analysis of 2 cohorts of IDH-wildtype GBM (42), a subset of cases with *MGMT* promoter methylation had significantly longer OS (but not progression-free survival [PFS]) than cases without *MGMT* methylation. Retrospective analysis of all available cases with *MGMT* data ($n = 1356$) reveals a significantly higher proportion of *MGMT* promoter methylation among GBM cases with LTS compared with cases with standard OS intervals (65.8% vs 33.9%, respectively; $p < 0.0001$; Table 2). Notably, in the cases with "very LTS" (VLTS), defined as $\geq$120-month survival (43), 77.8% of cases were positive for *MGMT* promoter methylation (39, 41, 43).

IDH1/2 MUTATION

First described in 2009 (4), astrocytomas with mutations in *IDH1/2* have been shown to have significantly longer PFS and OS in a grade-for-grade comparison with IDH-wildtype counterparts (3–6). The exact underlying mechanism of tumorigenesis following IDH mutation remains somewhat unclear; however, mutant *IDH1/2* results in the production of 2-hydroxyglutarate, an oncometabolite that can be detected by magnetic resonance spectroscopy (48, 49), and has been shown to induce epigenetic changes including widespread DNA hypermethylation (50, 51), as well as produce an alternate lengthening of telomeres phenotype in conjunction with characteristic *ATRX* and *TP53* mutation, which are found significantly more often in IDH-mutant cases (3, 52).

Although patients with IDH-mutant tumors have significantly longer postsurgical survival intervals, median survival for GBMs with this mutation remain at 24–31 months, and the majority of reported cases with IDH mutation do not survive beyond 3 years. However, numerous studies have reported that cohorts of LTS GBM patients are significantly enriched for *IDH1/2* mutations (24, 25, 30, 31, 36, 39, 41), although the percentage of LTS cases with IDH mutation varies greatly and this was not a universal finding (34, 53; Table 1). In the 11 studies that specifically included IDH mutation status ($n = 967$; 24, 25, 30, 31, 34, 36, 38, 39, 43, 53), 31.5% (84/267) LTS cases were IDH-mutant while only 4.6% (32/700) cases with STS harbored *IDH1/2* mutations ($p < 0.0001$; Table 2), despite large-scale studies indicating that IDH-mutant cases represent <10% of total GBM diagnoses. This finding suggests significant enrichment of LTS GBM cohort IDH-mutant cases. Notably, Marton et al (43) found that while there were not significantly more IDH mutations in their cohort of LTS GBMs, they did see a significantly higher rate of IDH mutation in 7 cases with OS $\geq$120 months, where 57.1% of cases were IDH-mutant compared with 22.7% of LTS cases and 7.1% of cases with survival under 36 months. In total, 63.6% VLTS cases (7/11) were IDH mutant (39, 41, 43). The rate of *MGMT* promoter hypermethylation was significantly

TABLE 1. Studies of Long-Term Survival in Glioblastoma.

Study Number	LTS n (Total n)	LTS Group Survival Range	Patient Age Range	Clinical, Radiologic, and Molecular Characteristics of LTS Cases	References
1	18 (123)	43–94 months	Age range = 22–64 years (median = 48 years)	*MGMT* promoter methylation more frequent in LTS cohort (11/14); Younger age associated with LTS	Sonoda et al (29)
2	11 (23)	37–85 months	Age range = 36–64 years (median = 52 years)	*IDH1* mutations more frequent in LTS cohort (9/11 vs 0/12); FABP5: CRABP2 mRNA expression ratio is significantly lower in LTS; Younger age associated with LTS	Barbus et al (24)
3	12 (42)	Median survival = 40.5 months	Age range = 13–59 years (median = 45.5 years)	*IDH1* mutation more frequent in LTS cohort (8/12 vs 8/30); *MGMT* promoter methylation more frequent in LTS cohort (10/12 vs 11/30)	Zhang et al (31)
4	69 (326)	52.8–94.5 months	Age range = 21–74 years (median = 49 years)	*IDH1* mutation more frequent in LTS cohort (23/67 vs 11/257); *MGMT* promoter methylation more frequent in LTS cohort (41/67 vs 85/257); Younger age associated with LTS	Hartmann et al (30)
5	28 (94)	Median survival = 50.4 months	Age range = 25–74 years (median = 52 years)	*IDH1* mutation more frequent in LTS cohort (10/28 vs 4/66); *MGMT* promoter methylation more frequent in LTS cohort (21/28 vs 20/66); Younger age associated with LTS	Reifenberger et al (25)
6	7 (7)	50.6–138.3 months	Age range = 32–70 years (median = 57 years)	All IDH wildtype; *MGMT* promoter methylation frequent in LTS cohort (5/7)	Gerber et al (33)
7	50 (100)	38.2–98.6 months	Average age = 51.9 years	Younger age and lack of subventricular zone involvement are associated with LTS; *MGMT* promoter methylation more frequent in LTS cohort (12/17 vs 4/11)	Adeberg et al (32)
8	10 (16)	41–83 months	Age range = 31–70 years (median = 59 years)	All IDH wildtype; 19+/20+ associated with LTS (in 16-case discovery cohort and in additional verification cohorts, n = 468)	Geisenberger et al (44)
9	17 (207)	3.1–7.9 years	Age range = 26–73 years (median = 51 years)	IDH-mutation frequency is not significantly different in LTS cohorts (1/17 vs 2/170); Younger age associated with LTS	Amelot et al (34)
10	40 (453)	Median survival > 48 months	Median = 50 years	IDH-mutation frequency is not significantly different in LTS cohorts (8/35)	Sarmiento et al (53)
11	40 (80)	Median survival = 58 months	Age range = 21–74 years (median = 47.5 years)	*IDH1* mutation more frequent in LTS cohort (6/40 vs 1/34); *MGMT* promoter methylation more frequent in LTS cohort (36/38 vs 12/33)	Smrdel et al (36)
12	1 (1)	78 months	57 years	*IDH1*-wildtype, *MGMT* promoter methylation, long-term risperidone use	Faraz et al (35)
13	24 (96)	>36 months	Average age = 43.7 years	*MGMT* promoter methylation, 19q loss, younger age, and lack of subventricular zone involvement are associated with LTS; IDH mutation is not significantly different in LTS cohorts (3/24 vs 1/49)	Nakagawa et al (38)
14	15 (77)	>36 months	Age range = 21–76 years (median = 49)	*MGMT* promoter methylation more frequent in LTS cohort (11/15 vs 24/62); lower levels of *FBLN4*, *IGFBP-2*, and *CHI3L1* associated with LTS; younger age associated with LTS	Li et al (37)
15	6 (93)	40.8–116.1 months	Age range = 29–61 years (median = 54.5 years)	Elevated CD34 expression was found in LTS; *MGMT* promoter methylation was more frequent in LTS	Michaelsen et al (40)
16	29 (74)	36–205 months	Age range = 22–72 years (median = 51 years)	*IDH1* mutations more frequent in LTS cohort (5/29 vs 0/45) and associated with better outcome	Cantero et al (39)
17	4 (4)	90–154 months	Age range = 37–60 years (median = 45.5 years)	All IDH mutant; *MGMT* promoter methylation in 1/4; *CCND2* high-level amplification in 3/4	Richardson et al (41)

(continued)

TABLE 1. Continued

Study Number	LTS n (Total n)	LTS Group Survival Range	Patient Age Range	Clinical, Radiologic, and Molecular Characteristics of LTS Cases	References
18	33 (119)	36–244 months	Age range = 19.8–78.3 years (median = 54.9 years for LTS; 42.2 years for VLTS)	*MGMT* promoter methylation and younger age associated with LTS; *MGMT* promoter methylation, younger age, *IDH1* mutation, and lack of *TERT* promoter mutation associated with VLTS (survival >120 months)	Marton et al (43)
19	51 (393)	36–88 months	Age range = 18–77 years (median = 54.5 years)	All IDH wildtype; lacking *EGFR* amplification, 7+/10-, and *TERT* promoter mutation (cIMPACT-NOW 3 factors), 19+/20+, and younger age associated with LTS	Galbraith et al (42)

LTS, long-term survival (≥36 months).

TABLE 2. Key Molecular Characteristics

Molecular Feature	GBM Subgroup	Frequency in LTS Cohort	Frequency in STS Cohort	p Value	References
MGMT promoter methylation	IDH-wildtype and -mutant GBM	65.8% (237/360)	33.9% (338/996)	$p < 0.0001$	(25, 29–44)
IDH1/2 mutation	IDH-wildtype and -mutant GBM	31.5% (84/267)	4.6% (32/700)	$p < 0.0001$	(24, 25, 30, 31, 34, 36, 38, 39, 41, 43, 53)
Loss of 19q	IDH-wildtype and -mutant GBM	33.3% (8/24)	8% (4/50)	$p = 0.0145$	(38)
19+/20+	IDH-wildtype GBM	33.3% (65/195)	11.6% (65/559)	$p < 0.0001$	(42, 44)
Absence of cIMPACT-NOW update 3 factors (*EGFR* amplification, 7+/10−, and *TERT* promoter mutation)	IDH-wildtype GBM	45.1% (23/51)	19.3% (66/342)	$p = 0.0001$	(42)
CCND2 amplification	IDH-mutant GBM	75% (3/4)			(41)

LTS, long-term survival (≥36 months); STS, short-term survival (<36 months).

higher in LTS cases in both IDH-mutant and -wildtype GBMs (33, 38, 39, 42–44, 46, 47, 49, 51).

MOLECULAR FACTORS WITHIN IDH-WILDTYPE GBM SUBGROUPS

There is currently debate over whether or not a true low-grade astrocytoma exists on the IDH-wildtype side (54–56), and numerous studies have shown that randomly selected IDH-wildtype lower grade astrocytomas and GBMs do not differ in terms of PFS or OS (16, 20, 56, 57). Lower grade IDH-wildtype astrocytomas (WHO grades II/III) with certain molecular features (*EGFR* amplification, 7+/10−, and/or *TERT* promoter mutation) display particularly aggressive behavior and are thus currently considered to be a molecular grade IV equivalent according to the cIMPACT-NOW update 3, despite the lack of grade IV histologic features (20). Our analysis (42) showed that in 2 cohorts, IDH-wildtype tumors that met the histologic criteria for GBM but lacked all 3 of these cIMPACT-NOW 3 factors (GBM-C0) had significantly longer recurrence-free survival (RFS; 17 vs 7 months, $p = 0.0008$) and OS (41 vs 15 months, $p < 0.0001$) than their counterparts with at least one of those molecular features (GBM-C1-3). These GBM-C0 cases also had a significantly younger age of onset (54.6 vs 62 years, $p < 0.0001$) and lower overall mutation burden ($p < 0.0001$). No significant difference was found between cases with varying single cIMPACT-NOW 3 factors, suggesting an statistically equivalent deleterious effect of each factor. This study demonstrated that GBM-C0 have statistically equivalent RFS and OS compared with IDH-wildtype lower grade gliomas without these cIMPACT-NOW update 3 molecular features (LGG-C0; 20, 56, 57). This suggests that there may truly be distinct "molecular grade III" and "molecular grade IV" variants of IDH-mutant astrocytoma that cannot be reliably distinguished by histologic features alone, although this must be confirmed in additional cohorts.

It has also previously been shown that IDH-wildtype GBMs with co-gain of chromosomes 19 and 20 (19+/20+) have significantly better OS than those without this alteration in discovery and multiple validation cohorts (44). 19+/20+ had no significant effect within GBM-C0 cohorts and was not statistically associated with lack of cIMPACT-NOW 3 factors; however, in cohorts with at least one cIMPACT-NOW factor (GBM-C1-3) there was significantly longer OS in cases with chromosome 19/20 co-gain than those without (42).

When these data were retrospectively reanalyzed to specifically address molecular features of histologic GBM cases

with survival ≥36 months (n = 51), there was a significantly greater proportion of LTS cases with 19+/20+ (31.3% vs 13.2%; univariate p = 0.0010; multivariate p = 0.0017) and lacking cIMPACT-NOW 3 factors (45.1% vs 19.3%; univariate p = 0.0001; multivariate p = 0.0005) compared with STS cases (n = 342). No significant difference was found in the proportion of cases with *MGMT* promoter methylation (41.3% vs 31.6%; univariate p = 0.2011; multivariate p = 0.1734). Accounting for overlap in some cases, there was a significantly higher percentage of LTS cases for which long survival could be "explained" by combining GBM-C0 status, 19+/20+, and *MGMT* (the percentage of cases positive for at least one of these findings) compared with the STS cohort (84.3% vs 50%, respectively; p < 0.0001). It should be noted, however, that none of these molecular features is a guarantee of longer survival, as there were more raw examples of GBM-C0 status (66 vs 23), 19+/20+ (32 vs 10), and *MGMT* promoter methylation (108 vs 21) in cases with <36-month survival. Several other factors have also been suggested as important in LTS cohorts, including younger age at onset (although median ages tend to be older than IDH-mutant cases) although this may not be independent of molecular features (42, 58) and may vary depending on geographic location (59).

MOLECULAR FACTORS WITHIN IDH-MUTANT GBM SUBGROUPS

IDH-mutant GBM occurs significantly less frequently than IDH-wildtype GBM, with most studies agreeing that <10% of GBM diagnoses have IDH mutation. Despite comprising a significant percentage of LTS cases (Table 2), many large-scale cohorts have relatively few profiled examples of IDH-mutant GBM; for example, the TCGA database includes only 24 confirmed cases of IDH-mutant GBM with full molecular profiling (4.2% of total GBM cases; 10, 11). It is also important to note that while IDH-mutant GBMs make up a disproportionate fraction of cases with LTS, the majority of IDH-mutant cases have survival <36 months, so this mutation is also no guarantee of longer OS (or later recurrences).

Nevertheless, a few key molecular trends can be identified within the available literature. Like their IDH-wildtype counterparts, IDH-mutant GBM cases with long survival have higher frequencies of *MGMT* promoter methylation, and, in one study, all IDH-mutant cases with survival ≥120 months also had *MGMT* methylation, suggesting that the combination of these 2 molecular factors may have an additive effect on postoperative survival times (43). In addition, in a small study of IDH-mutant GBM patients with >7.5 years OS (and no documented recurrence or neurologic impairment), 3/4 cases had high-level *CCND2* amplification, a feature not observed in TCGA data of IDH-wildtype GBM patients (41). The frequency of this alteration in this small sample suggests that *CCND2* amplification may be a significant feature associated with longer survival in a minority of IDH-mutant GBMs; however, the underlying mechanism is unclear. *CCND2* amplification is significantly more common in lower grade astrocytomas and gemistocytic subtypes of IDH-mutant astrocytomas (60), and may act through pep5, a cyclin D2-derived peptide that has been shown to induce apoptosis in some in vitro studies, reduce tumor volume in animal models, and data suggest that in some cancers it may halt the S/G2 transition of the cell cycle (61, 62). Unlike IDH-mutant lower grade astrocytomas, molecular features associated with worse OS, including *CDK4* amplification and homozygous *CDKN2A/B* deletion do not appear to have a significant affect, although these alterations are significantly more frequent in grade IV tumors compared with lower grade counterparts (9, 11, 15, 16).

ADDITIONAL FEATURES IN LONG-TERM GBM SURVIVORS

Additional findings in multiple studies have shown that younger age at initial diagnosis is associated with significantly longer OS in GBM (24, 25, 29, 30, 32, 34, 37, 38, 42, 43). IDH-mutant GBMs present in younger patients, so some of this effect can be accounted for by this mutation; however, in 2 independent IDH-wildtype cohorts, younger age at diagnosis was associated with lack of cIMPACT-NOW update 3 factors and better OS in a multivariate cox proportional hazard regression model. This suggests that younger age may also be a beneficial prognostic factor within IDH-wildtype subsets as well (42), although some data suggest there may be other confounding variables associated with age in certain cohorts (63). Other less-studied factors that have been proposed as beneficial factors in select cohorts of LTS GBM include lack of subventricular zone involvement (32, 38), 19q loss (38), elevated CD34 expression levels (40), FABP5: CRABP2 mRNA expression ratios (24), decreased expression of CHI3L1, FBLN4, and IGFBP-2 (37), certain immune factors (64), and methylation signatures in IDH-mutant GBM (65).

CONCLUSIONS

In conclusion, despite significant progress in identifying multiple molecular features associated with aggressive behavior in subsets of histologically lower grade astrocytomas, less progress has been made thus far in identifying genetic factors associated with long survival in histologically defined GBMs. A review of the current literature suggests that the molecular background of LTS GBM cases is complex and no one molecular feature may be associated with survival ≥36 months. Despite this, there are a number of factors that appear to be significantly more common in GBM cases with long survival: *MGMT* promoter hypermethylation (p < 0.0001), *IDH1/2* mutation (p < 0.0001), and loss of 19q (p = 0.0145), and in IDH-wildtype GBM cases with long survival: 19+/20+ (p < 0.0001) and absence of cIMPACT-NOW update 3 factors (p = 0.0001). None of these factors alone appear sufficient to confer better clinical outcome; however, as these features are also found with relative frequency in GBMs with significantly shorter survival times. More work is needed on this topic, and full molecular characterization of large cohorts of both IDH-wildtype and -mutant GBMs, focusing on those with long survival, is needed to further characterize this rare tumor subset, both to identify patients with better odds of longer survival and to better understand the complex underlying biology of GBM for better therapeutic design. GBM remains a devastating diagnosis with dismal outcomes despite some advances in

therapy; however, identification of cases with better outcomes and increasing understanding of the underlying genetics involved gives hope of finding additional molecular features that may serve as prognostic markers and potential future therapeutic targets.

REFERENCES

1. Ostrom QT, Cioffi G, Gittleman H, et al. CBTRUS Statistical Report: Primary brain and other central nervous system tumors diagnosed in the United States in 2012-2016. Neuro Oncol 2019;21:v1–100
2. Louis DN, Ohgaki H, Wiestler OD, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol 2007;114: 97–109
3. 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;131:803–20
4. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765–73
5. 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
6. Chen JR, Yao Y, Xu HZ, et al. Isocitrate dehydrogenase (IDH)1/2 mutations as prognostic markers in patients with glioblastomas. Medicine (Baltimore) 2016;95:e2583
7. Mirchia K, Richardson TE. Beyond IDH-mutation: Emerging molecular diagnostic and prognostic features in adult diffuse gliomas. Cancers (Basel) 2020;12:1817
8. Cohen A, Sato M, Aldape K, et al. DNA copy number analysis of Grade II-III and Grade IV gliomas reveals differences in molecular ontogeny including chromothripsis associated with IDH mutation status. Acta Neuropathol Commun 2015;3:34
9. Reis GF, Pekmezci M, Hansen HM, et al. CDKN2A loss is associated with shortened overall survival in lower-grade (World Health Organization Grades II-III) astrocytomas. J Neuropathol Exp Neurol 2015;74: 442–52
10. Ceccarelli M, Barthel FP, Malta TM, et al. Molecular profiling reveals biologically discrete subsets and pathways of progression in diffuse glioma. Cell 2016;164:550–63
11. Cimino PJ, Zager M, McFerrin L, et al. Multidimensional scaling of diffuse gliomas: Application to the 2016 World Health Organization classification system with prognostically relevant molecular subtype discovery. Acta Neuropathol Commun 2017;5:39
12. Richardson TE, Snuderl M, Serrano J, et al. Rapid progression to glioblastoma in a subset of IDH-mutated astrocytomas: A genome-wide analysis. J Neurooncol 2017;133:183–92
13. Richardson TE, Sathe AA, Kanchwala M, et al. Genetic and epigenetic features of rapidly progressing IDH-mutant astrocytomas. J Neuropathol Exp Neurol 2018;77:542–8
14. Shirahata M, Ono T, Stichel D, et al. Novel, improved grading system(s) for IDH-mutant astrocytic gliomas. Acta Neuropathol 2018;136:153–66
15. Cimino PJ, Holland EC. Targeted copy number analysis outperforms histologic grading in predicting patient survival for WHO grades II/III IDH-mutant astrocytomas. Neuro Oncol 2019;21:819–21
16. Mirchia K, Sathe AA, Walker JM, et al. Total copy number variation as a prognostic factor in adult astrocytoma subtypes. Acta Neuropathol Commun 2019;7:92
17. Mirchia K, Snuderl M, Galbraith K, et al. Establishing a prognostic threshold for total copy number variation within adult IDH-mutant grade II/III astrocytomas. Acta Neuropathol Commun 2019;7:121
18. Richardson TE, Walker JM. The prognostic significance of RB1 and PI3K pathway alterations in IDH-mutant grade II/III astrocytomas. J Neuropathol Exp Neurol 2020.
19. Louis DN, Giannini C, Capper D, et al. cIMPACT-NOW update 2: Diagnostic clarifications for diffuse midline glioma, H3 K27M-mutant and diffuse astrocytoma/anaplastic astrocytoma, IDH-mutant. Acta Neuropathol 2018;135:639–42
20. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 3: Recommended diagnostic criteria for "Diffuse astrocytic glioma, IDH-wildtype, with molecular features of glioblastoma, WHO grade IV". Acta Neuropathol 2018;136:805–10
21. Brat DJ, Aldape K, Colman H, et al. cIMPACT-NOW update 5: Recommended grading criteria and terminologies for IDH-mutant astrocytomas. Acta Neuropathol 2020;139:603–8
22. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. Cell 2013;155:462–77
23. Lara-Velazquez M, Al-Kharboosh R, Jeanneret S, et al. Advances in brain tumor surgery for glioblastoma in adults. Brain Sci 2017;7:166.
24. Barbus S, Tews B, Karra D, et al. Differential retinoic acid signaling in tumors of long- and short-term glioblastoma survivors. J Natl Cancer Inst 2011;103:598–606
25. Reifenberger G, Weber RG, Riehmer V, et al.; for the German Glioma Network. Molecular characterization of long-term survivors of glioblastoma using genome- and transcriptome-wide profiling. Int J Cancer 2014;135:1822–31.
26. Peng S, Dhruv H, Armstrong B, et al. Integrated genomic analysis of survival outliers in glioblastoma. Neuro Oncol 2017;19:833–44
27. Netsky MG, August B, Fowler W. The longevity of patients with glioblastoma multiforme. J Neurosurg 1950;7:261–9
28. Elvidge AR, Barone BM. Long-term postoperative survival in two cases of glioblastoma multiforme. J Neurosurg 1965;22:382–6
29. Sonoda Y, Kumabe T, Watanabe M, et al. Long-term survivors of glioblastoma: Clinical features and molecular analysis. Acta Neurochir 2009;151:1349–58
30. Hartmann C, Hentschel B, Simon M, et al.; for the German Glioma Network. Long-term survival in primary glioblastoma with versus without isocitrate dehydrogenase mutations. Clin Cancer Res 2013;19:5146–57.
31. Zhang GB, Cui XL, Sui DL, et al. Differential molecular genetic analysis in glioblastoma multiforme of long- and short-term survivors: A clinical study in Chinese patients. J Neurooncol 2013;113:251–8
32. Adeberg S, Bostel T, Konig L, et al. A comparison of long-term survivors and short-term survivors with glioblastoma, subventricular zone involvement: A predictive factor for survival? Radiat Oncol 2014;9:95
33. Gerber NK, Goenka A, Turcan S, et al. Transcriptional diversity of long-term glioblastoma survivors. Neuro Oncol 2014;16:1186–95
34. Amelot A, De Cremoux P, Quillien V, et al. IDH-mutation is a weak predictor of long-term survival in glioblastoma patients. PLoS One 2015;10: e0130596
35. Faraz S, Pannullo S, Rosenblum M, et al. Long-term survival in a patient with glioblastoma on antipsychotic therapy for schizophrenia: A case report and literature review. Ther Adv Med Oncol 2016;8:421–8
36. Smrdel U, Popovic M, Zwitter M, et al. Long-term survival in glioblastoma: Methyl guanine methyl transferase (MGMT) promoter methylation as independent favourable prognostic factor. Radiol Oncol 2016;50: 394–401
37. Li F, Li Y, Zhang K, et al. FBLN4 as candidate gene associated with long-term and short-term survival with primary glioblastoma. Onco Targets Ther 2017;10:387–95
38. Nakagawa Y, Sasaki H, Ohara K, et al. Clinical and molecular prognostic factors for long-term survival of patients with glioblastomas in single-institutional consecutive cohort. World Neurosurg 2017;106:165–73
39. Cantero D, Rodriguez de Lope A, Moreno de la Presa R, et al. Molecular study of long-term survivors of glioblastoma by gene-targeted next-generation sequencing. J Neuropathol Exp Neurol 2018;77:710–6
40. Michaelsen SR, Urup T, Olsen LR, et al. Molecular profiling of short-term and long-term surviving patients identifies CD34 mRNA level as prognostic for glioblastoma survival. J Neurooncol 2018;137:533–42
41. Richardson TE, Patel S, Serrano J, et al. Genome-wide analysis of glioblastoma patients with unexpectedly long survival. J Neuropathol Exp Neurol 2019;78:501–7
42. Galbraith K, Kumar A, Abdullah KG, et al. Molecular correlates of long survival in IDH-wildtype glioblastoma cohorts. J Neuropathol Exp Neurol 2020;79:843–54
43. Marton E, Giordan E, Siddi F, et al. Over ten years overall survival in glioblastoma: A different disease? J Neurol Sci 2020;408:116518
44. Geisenberger C, Mock A, Warta R, et al. Molecular profiling of long-term survivors identifies a subgroup of glioblastoma characterized by chromosome 19/20 co-gain. Acta Neuropathol 2015;130:419–34
45. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352: 997–1003
46. Weller M, Tabatabai G, Kastner B, et al.; for the DIRECTOR Study Group. MGMT promoter methylation is a strong prognostic biomarker

for benefit from dose-intensified temozolomide rechallenge in progressive glioblastoma: The DIRECTOR Trial. Clin Cancer Res 2015;21:2057–64.
47. Binabaj MM, Bahrami A, ShahidSales S, et al. The prognostic value of MGMT promoter methylation in glioblastoma: A meta-analysis of clinical trials. J Cell Physiol 2018;233:378–86
48. Dang L, White DW, Gross S, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature 2009;462:739–44
49. Choi C, Ganji SK, DeBerardinis RJ, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012;18:624–9
50. Lu C, Ward PS, Kapoor GS, et al. IDH mutation impairs histone demethylation and results in a block to cell differentiation. Nature 2012;483:474–8
51. Turcan S, Rohle D, Goenka A, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature 2012;483:479–83
52. Reuss DE, Sahm F, Schrimpf D, et al. ATRX and IDH1-R132H immunohistochemistry with subsequent copy number analysis and IDH sequencing as a basis for an "integrated" diagnostic approach for adult astrocytoma, oligodendroglioma and glioblastoma. Acta Neuropathol 2015;129:133–46
5. Sarmiento JM, Mukherjee D, Black KL, et al. Do long-term survivor primary glioblastoma patients harbor IDH1 mutations? J Neurol Surg A Cent Eur Neurosurg 2016;77:195–200
54. Aibaidula A, Chan AK, Shi Z, et al. Adult IDH wild-type lower-grade gliomas should be further stratified. Neuro Oncol 2017;19:1327–37
55. Reuss DE, Kratz A, Sahm F, et al. Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities. Acta Neuropathol 2015;130:407–17
56. Weller M, Weber RG, Willscher E, et al. Molecular classification of diffuse cerebral WHO grade II/III gliomas using genome- and transcriptome-wide profiling improves stratification of prognostically distinct patient groups. Acta Neuropathol 2015;129:679–93
57. Stichel D, Ebrahimi A, Reuss D, et al. Distribution of EGFR amplification, combined chromosome 7 gain and chromosome 10 loss, and TERT promoter mutation in brain tumors and their potential for the reclassification of IDHwt astrocytoma to glioblastoma. Acta Neuropathol 2018;136:793–803
58. Hwang T, Mathios D, McDonald KL, et al. Integrative analysis of DNA methylation suggests down-regulation of oncogenic pathways and reduced somatic mutation rates in survival outliers of glioblastoma. Acta Neuropathol Commun 2019;7:88
59. Umehara T, Arita H, Yoshioka E, et al. Distribution differences in prognostic copy number alteration profiles in IDH-wild-type glioblastoma cause survival discrepancies across cohorts. Acta Neuropathol Commun 2019;7:99
60. Sahm F, Korshunov A, Schrimpf D, et al. Gain of 12p encompassing CCND2 is associated with gemistocytic histology in IDH mutant astrocytomas. Acta Neuropathol 2017;133:325–7
61. de Araujo CB, Russo LC, Castro LM, et al. A novel intracellular peptide derived from g1/s cyclin d2 induces cell death. J Biol Chem 2014;289:16711–26
62. Russo LC, Araujo CB, Iwai LK, et al. A Cyclin D2-derived peptide acts on specific cell cycle phases by activating ERK1/2 to cause the death of breast cancer cells. J Proteomics 2017;151:24–32
63. Gately L, Collins A, Murphy M, et al. Age alone is not a predictor for survival in glioblastoma. J Neurooncol 2016;129:479–85
64. Czapski B, Baluszek S, Herold-Mende C, et al. Clinical and immunological correlates of long term survival in glioblastoma. Contemp Oncol (Pozn) 2018;22:81–5
65. Shinawi T, Hill VK, Krex D, et al. DNA methylation profiles of long- and short-term glioblastoma survivors. Epigenetics 2013;8:149–56