Epidemiology and Outcome of Glioblastoma

AHMAD FALEH TAMIMI1 • MALIK JUWEID2

1Department of Neurosurgery, Jordan University Hospital and Medical School, University of Jordan, Amman, Jordan; 2Department of Radiology and Nuclear Medicine, Jordan University Hospital and Medical School, University of Jordan, Amman, Jordan

Author for correspondence: Ahmad Faleh Tamimi, Department of Neurosurgery, Jordan University Hospital and Medical School, University of Jordan, Amman, Jordan. E-mail: aftamimi@hotmail.com

Doi: http://dx.doi.org/10.15586/codon.glioblastoma.2017.ch8

Abstract: Glioblastoma (GBM) is the most aggressive malignant primary brain tumor. With an incidence rate of 3.19 per 100,000 persons in the United States and a median age of 64 years, it is uncommon in children. The incidence is 1.6 times higher in males compared to females and 2.0 times higher in Caucasians compared to Africans and Afro-Americans, with lower incidence in Asians and American Indians. GBM is commonly located in the supratentorial region (frontal, temporal, parietal, and occipital lobes) and is rarely located in cerebellum. Genetic and environmental factors have been investigated in GBM. Risk factors include prior radiotherapy, decreased susceptibility to allergy, immune factors and immune genes, as well as some single nucleotide polymorphisms detected by genomic analysis. Use of anti-inflammatory medication has been found to be protective against GBM. Survival from GBM is poor; only few patients survive 2.5 years and less than 5% of patients survive 5 years following diagnosis. Survival rates for patients with GBM have shown no notable improvement in population statistics in the last three decades. Molecular epidemiology integrates molecular technology into epidemiological studies and outcomes. The future of the epidemiology of
GBM will depend on multicenter studies generating large clinical data sets of genomic data potentially leading to further understanding of the roles of genes and environment in the development of this devastating disease.

Key words: Brain tumors; Epidemiology; Glioblastoma; Outcome.

Introduction

Glioblastoma (GBM) is the most aggressive diffuse glioma of astrocytic lineage and is considered a grade IV glioma based on the WHO classification (1). GBM is the most common malignant primary brain tumor making up 54% of all gliomas and 16% of all primary brain tumors (2). GBM remains an incurable tumor with a median survival of only 15 months (3). Treatment is complex, initially consisting of maximally safe surgical resection followed by radiation therapy (RT) and concurrent Temozolomide (TMZ) chemotherapy (4). The terms “primary GBM” and “secondary GBM” were first used by the German neuropathologist Hans Joachim Sherer in Antwerp in 1940 (5). Nowadays, GBM comprised of primary and secondary types, constituting distinct disease entities which evolve through different genetic pathways, affect patients at different ages, and likely differ in prognosis and response to therapy (5). Primary de novo GBM accounts for more than 80% of GBM (6), occurs in older patients (mean age = 64 years), and typically shows epidermal growth factor receptor (EGFR) over expression, PTN (MMC I) mutation, CDKN2A (p16) deletion, and less frequently MDM2 amplification. Secondary GBM develops from lower grade astrocytoma or oligodendrogliomas, occurs in younger patients (mean age = 45 years), and often contains TP53 mutations as the earliest detectable alteration (5). Mutations in isocitrate dehydrogenase-1 (IDH1) and IDH2 are present in 70–80% of low-grade glioma and secondary GBM, and in only 5–10% of primary GBM (7–9). Strong link has been found between IDH mutations and genome-wide glioma cytosine–phosphate–guanine I and methylator phenotype (G-CIMP) across all subtypes of glioma (10). The WHO recently added a rare subtype of GBM termed “GBM-0,” with oligodendroglioma component, defined as GBM having areas resembling anaplastic oligodendroglioma, with features of GBM and necrosis without microvascular proliferation (7). According to the 2016 WHO classification of GBM multiforme, this tumor has been separated from the classical identity and is currently classified into three groups: GBM IDH-wild type (including giant cell GBM, gliosarcoma, and epithelioid GBM), GBM IDH-mutant, and GBM NOS (1). The average annual age-adjusted incidence rate (IR) of GBM is 3.19 per 100,000 persons in the United States (11), with the age-adjusted GBM rates being 2.5 times higher in European Americans than in African Americans (12).

Incidence of Glioblastoma

The average annual age-adjusted IR of GBM is variable, ranging from 0.59 per 100,000 persons to 3.69 per 100,000 persons (11, 13–17), and is the highest among malignant primary brain tumors (Table 1).
AGE

GBM is primarily diagnosed at older age with a median age of 64 at diagnosis (2, 18). The incidence increases with age peaking at 75–84 years and drops after 85 years (2). The age at diagnosis tends to be higher for primary GBM (mean age of 55 and median age of 64) (2, 18) than for secondary GBM (mean age of 40 years) (19). GBM is uncommon in children (2). DNA methylation patterns for pediatric and adult groups are similar, but there are distinct clusters that are predominantly found in children and adolescents. Two of these correspond strictly to recurrent age-specific mutations in H3F3A. Another type was enriched for DPGFRA alterations and consists of patients from a more widespread age range (20). Age-adjusted and age-specific IRs for GBM according to age at diagnosis and gender are shown in Figure 1 (11).

GENDER AND SITE

Overall, the incidence of GBM is higher in males than in females (3.97 vs. 2.53 in the United States) (2). The male-to-female ratio is increased for each brain subsite except for the posterior fossa (18). The IR of primary GBMs is higher in men with reported male-to-female ratio of 1:0.33, while the IR of secondary GBMs is higher in women with reported male-to-female ratio of 0.65:1 (20).

GBM is most commonly located in the supratentorial region (frontal, temporal parietal, and occipital lobes), with the highest incidence in the frontal lobe, multiple lobes (overlapping tumors), followed by the temporal and parietal lobes (18). GBM is rarely located in the cerebellum and is very rare in the spinal cord (21, 22), with different tumor behavior found at these locations (21). Cerebellar location of GBM is more common in younger patients (50–56 years of age); supratentorial location is prevalent in older patients (62-64 years of age) and cerebellar location is rare (0.4–3.4%) in this age bracket (23). Cerebellar GBM is less common in Whites and is smaller in size (22–24). For spinal cord GBMs, the mean age is 27 years, with a male predominance; 53% of these tumors are seen in those aged less than 18 years (25).
ETNICITY AND GENETICS

Whites have the highest IR of GBM followed by Blacks; age-adjusted GBM rate is 2.5 times higher in European Americans than in African Americans and more common in non-Hispanics than in Hispanics (12) (Figure 2) (11). Associations between XRCC1 polymorphisms and glioma are still controversial. However, a recent meta-analysis showed that the Arg399Gln polymorphism was associated with an increased risk of glioma in Asians and of GBM in Caucasians. However, Arg194Trp/Arg280His polymorphisms probably have no influence on glioma in different ethnicities (26).

There is increased incidence of GBM in patients with hereditary tumor syndromes, for example, Turcot syndrome (27) and Li-Fraumeni syndrome (5). Otherwise, GBM occurs sporadically without known genetic predisposition (28).

Classification of GBM

GBM is a grade IV glioma according to the WHO 2007 classification and is the most common and lethal primary malignancy of the central nervous system. Despite multidisciplinary treatments such as surgery, chemotherapy, and radiotherapy, the median survival time for patients with GBM is only 14.6 months (4). Due to its high degree of invasiveness, radical tumor resection is not curative.
There is experimental evidence that GBM contains a subpopulation of highly tumorigenic cells (GBM stem cells) from which recurrent GBM is thought to derive (29–31), and that GBM has the capacity to differentiate into multiple lineages of tumor genesis (29, 31, 32).

As stated above, GBMs can be classified into primary and secondary GBMs. Primary GBM occurs de novo without evidence of a less malignant precursor, whereas secondary GBM develops from initially low-grade diffuse astrocytoma (WHO grade II diffuse astrocytoma) or anaplastic astrocytoma (Grade III). The majority of GBMs (90%) are primary (33), and patients with primary GBM tend to be older (mean age = 55 years) than those with secondary GBM (mean age = 40 years). Genetic alterations more typical for primary GBM are EGFR overexpression, PTN mutation, and loss of chromosome 10 (5, 6, 34, 35), whereas genetic alterations more commonly seen in secondary GBM include IDH1 mutations, TP53 mutations, and 19q loss (5, 6, 20, 36–39). IDH1 mutation is associated with better outcome and increased overall survival (33). Interestingly, IDH1 mutations are also found in 80% of diffuse astrocytoma and anaplastic astrocytoma, the precursors of secondary GBM, and in less than 5% of primary GBM (8, 40–42). Thus, the IDH1 mutation is a reliable objective molecular marker for secondary GBM over clinical and pathological criteria (33).

Molecular diagnosis will contribute to a better understanding and classification of brain tumors (42). The classification of GBM based on gene expression distinguishes between four subtypes: proneural, neural, classical, and mesenchymal. Aberrations and gene expression of EGFR, NF1, and PDGFRA/IDH1 define classical, mesenchymal, and proneural GBMs, respectively. Genes of normal brain cell types show a strong relationship between subtypes and different neural lineages.
and the response to aggressive treatment differs by subtype, with prominent benefits in the classical and little or no benefit in the proneural subtype (35). GBMs have significant genetic heterogeneity and tumor subtypes with genetic alterations, which carry prognostic significance (5). In 2010, GBM was classified into four different molecular subtypes (35): classical, mesenchymal, proneural, and neural subtypes based on characteristic genetic alterations and distinct molecular profiles (33, 42–44). Each subtype harbors distinct genetic alterations and expression profiles (42, 44). Loss of chromosomal 10 is frequently observed in classical subtype as well as mutations in TP53 and IDH1. The mesenchymal subtype is enriched in the gene expression pattern of astrocytes as well as microglial markers. Proneural subtype is enriched in proneural genes expressed in oligodendrocytes and characterized by alterations in TP53, platelet-derived growth receptor (PDGFR), and ILDH1 (5, 8, 35–37). The proneural subtype is also associated with younger age at diagnosis (31). Neural subtype is the most similar to the astrocytic and oligodendrocytic markers. Finally, a group with only telomerase reverse transcripts (TERT) mutation is found in primarily grade IV gliomas (45). According to the 2016 WHO classification of CNS tumors, GBM is divided into the following groups:

(i) GBM, IDH-wild type (about 90% of cases) corresponding most frequently to the clinically defined primary or de novo GBM and predominant in patients aged over 55 years (5, 33).
(ii) GBM, IDH-mutant (about 10% of cases) corresponding closely to the so-called secondary GBM, with a history of prior lower grade diffuse glioma, and preferentially occurring in younger patients (5, 33).
(iii) GBM, NOS, a diagnosis that is reserved for those tumors for which full IDH evaluation cannot be performed.

One provisional new variant of GBM has been added to the classification: epithelioid GBM. It joins giant cell GBM and gliosarcoma under the umbrella of IDH-wild type GBM. Epithelioid GBM features large epithelioid cells, with abundant eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli (often resembling melanoma cells), and variably present rhabdoid cells. GBM with primitive neuronal component was added as a pattern in GBM. This pattern, previously referred to in the literature as GBM with PNET-like component, usually comprised of a diffuse astrocytoma of any grade (or oligodendroglioma in rare cases) that has well-demarcated nodules containing primitive cells that display neuronal differentiation, and sometimes has MYC or MYCN amplification. These tumors also have a tendency for craniospinal fluid dissemination (46). About a quarter of them develop in patients with a previously known lower grade glioma precursor, a subset of which shows R132H IDH1 immunoreactivity in both the glial and primitive neuronal components (47).

## Survival and Prognostic Factors

### RISK FACTORS

Factors associated with GBM risk are prior radiation, decreased susceptibility to allergy, immune factors and immune genes, and some nucleotide polymorphisms, detected by genome-wide association (48, 49). The lower risk of GBM in people with
asthma and other allergic conditions is consistent with findings that have been confirmed by objective evidence from asthma and other allergies-related germline polymorphism in patients with GBM and in controls. Genotypes that increase asthma risk are associated with decreased GBM risk (49). Nevertheless, both familiar aggregation of glioma and the inverse association of allergies and immune-related conditions with glioma have been shown consistently (48). A lower risk of gliomas has been associated with allergy or atopic disease (e.g., asthma, eczema, psoriasis) (50–52). A short-term (less than 10 years) use of anti-inflammatory medication is also associated with a protective effect against GBM (52). The use of cyclooxygenase-2 (COX-2) inhibitors is still controversial where a positive effect in laboratory investigation in reducing the gliomagenesis was achieved in vivo and in vitro (53). However, in clinical setting, the use of COX-2 inhibitor was unrelated to glioma risk (54).

Other factors associated with GBM risk are high socioeconomic status and a person's height (18, 55). There is no substantial evidence of GBM association with lifestyle characteristics, such as cigarette smoking, alcohol consumption, drug use, or dietary exposure to nitrous compounds (56). Inconsistent and indefinite reports have been published regarding the association of GBM with the use of mobile phones (57, 58). Prognostic factors that affect the survival of GBM patients include the resectability of the tumor, its location, size, multifocality, as well as advanced age, comorbidities, and the patient's general condition (59).

### Outcome and Prognostic Factors

GBM is an aggressive neoplasm with a median survival of only 3 months in untreated patients (60). Surgery remains an important component in the management of GBM. Surgery enables a histological confirmation of the clinical diagnosis and also has decompressive and cytoreductive effects, with an advantage of increased survival with complete resection (61). Tumor fluorescence derived from 5 aminolevulinic acid enabled a more complete resection of contrast-enhancing tumor, leading to improved progression-free-survival in patients with GBM (61). The main contraindications to resective surgery are poor performance status (Karnofsky of less than 70), advanced age, and eloquent location (19). The combination of radiotherapy and TMZ chemotherapy is the most effective adjuvant therapy shown to prolong survival following primary resection. Radiotherapy followed by TMZ results in significantly prolonged survival compared with radiotherapy alone (4). Treatment of GBM remains challenging. The current experience in GBM treatment shows that several targets should be approached. Therefore, rational combinations between established treatments and new approaches aiming, for example, at inhibition of angiogenesis, induction of apoptosis, or inhibition of several signal transduction pathways might offer the best opportunity to improve prognosis.

### Conclusion

GBM is still the most malignant primary brain tumor with clear predominance in males. The management and outcome of GBM have remained stable for almost the last four decades. However, resent advances in genetic and molecular research
will open a new horizon in the future of management and outcome of this devastating tumor.

Conflict of interest: The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this manuscript.

Copyright and permission statement: To the best of our knowledge, the materials included in this chapter do not violate copyright laws. All original sources have been appropriately acknowledged and/or referenced. Where relevant, appropriate permissions have been obtained from the original copyright holder(s).

References

1. Louis N, Perry A, Reifenberge RG, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization classification of tumors of the central nervous system: A summary. Acta Neuropathol. 2016;131:803–20. http://dx.doi.org/10.1007/s00401-016-1545-1
2. Ostrom QT, Gittleman H, Farah F, Ondracek A, Chen Y, Wolinsky Y, et al. CBTRUS statistical report: Primary brain and central nervous system tumors diagnosed in the United States in 2006–2010. Neuro Oncol. 2013;15(Suppl):2ii–56.
3. Koshy M, Villano JL, Dolecek TA, Howard A, Mahmood U, Chmura SJ, et al. Improved survival time trends of glioblastoma using the SEER 17 population-based registries. J Neuro Oncol. 2012;107(1):207–12. http://dx.doi.org/10.1007/s11060-011-0738-7
4. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant Temozolomide for glioblastoma. N Engl J Med. 2005;352:987–96. http://dx.doi.org/10.1056/NEJMoa043330
5. Kleihues P, Ohgaki H. Primary and secondary glioblastomas: From concept to clinical diagnosis. Neuro Oncol. 1999;1:44–51. http://dx.doi.org/10.1215/15228517-1-1-44
6. Ohgaki H, Dessen P, Joude B, Horstmann S, Nishikawa T, Di Patre PL, et al. Genetic pathways to glioblastoma: A population-based study. Cancer Res. 2004;64:6892–9. http://dx.doi.org/10.1158/0008-5472.CAN-04-1337
7. Appin CL, Gao J, Chisolm C, Torian M, Alexis D, Vincentelli C, et al. Glioblastoma with oligodendro-glioma component(GMB-O) molecular genetic and clinical characteristics. Brain Pathol. 2013;23(4):454–61. http://dx.doi.org/10.1111/bpa.12018
8. Yan H, Parsons DW, Jin G, McLendon R, Rasheed BA, Yuan W IDH1 and IDH2 mutations in gliomas. N Engl J Med. 2009;360:765–73. http://dx.doi.org/10.1056/NEJMoa0808710
9. Hartmann C, Hentschel B, Wick W, Capper D, Felsberg J, Simon M, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1mutation status accounts for the unfavorable prognostic effect of higher age: Implications for classification of gliomas. Acta Neuropathol. 2010;120:707–18. http://dx.doi.org/10.1007/s00401-010-0781-z
10. Noushmehr H, Weisenberger DJ, Diefes K, Phillips HS, Pujara K, Berman BP, et al. Identification of a CpG island methylator phenotype that defines a distinct subgroup of glioma. Cancer Cell. 2010;17(5):510–22. http://dx.doi.org/10.1016/j.ccr.2010.03.017
11. Thakkar J, Dolecek TA, Horbinski C, Ostrom QT, Lightner DD, Barnholtz-Sloan JS, et al. Epidemiologic and molecular prognostic review of glioblastoma. Cancer Epidemiol. Biomarkers Rev. 2014;23(10):1985–96. http://dx.doi.org/10.1158/1055-9965.EPI-14-0275
12. Song W, Ruder AM, Hu L, Li Y, Ni R, Shao W, et al. Genetic epidemiology of glioblastoma multiforme: Confirmatory and new findings from analyses of human leukocyte antigen alleles and motifs. PLoS One. 2009 Sept 23;4(9):e7157.
13. Dobes M, Khurana VG, Shadbolt TB, Smith SF, Sme R, Dexter M, et al. Increasing incidence of glioblastoma and meningioma, and decreasing incidence of Schwanoma (2000–2008); Findings of a multicentric Australian study. Surg Neurol Int. 2011;2:176. http://dx.doi.org/10.4103/2152-7806.90696
14. Arora RS, Alston RD, Eden TO, Estlin EJ, Moran A, Birch JM. Age-incidence patterns of primary CNS tumors in children, adolescents, and adults in England. Neuro Oncol. 2009;11(4):403–13. http://dx.doi.org/10.1215/15228517-2008-097

15. Lee CH, Jung KW, Yoo H, Park S, Lee SH. Epidemiology of primary brain and central nervous system tumors in Korea. J Korean Neurosurg Soc. 2010;48(2):145–52. http://dx.doi.org/10.3340/jkns.2010.48.2.145

16. Tamimi AF, Tamimi I, Abdelaziz M, Saleh Q, Obeidat F, Al-Husseini M, et al. Epidemiology of malignant and non-malignant primary brain tumors in Jordan. Neuroepidemiology. 2015;45:100–8. http://dx.doi.org/10.1159/000438926

17. Gausia SK, Markou M, Voulgaris S, Bai M, Polyzoikis K, Kyritsis A, et al. Descriptive epidemiology of cerebral gliomas in northwest Greece and study of potential predisposing factors, 2005–2007. Neuroepidemiology. 2009;33(2):89–95. http://dx.doi.org/10.1159/000222090

18. Chakrabarti I, Cockburn M, Cozen W, Wang YP, Preston-Martin S. A population-based description of glioblastoma multiforme in Los Angeles County, 1974–1999. Cancer. 2005;104:2798–806. http://dx.doi.org/10.1002/cncr.21539

19. Taylor A, Karajannis MA, Harter DH. Glioblastoma multiforme: State of art and future therapeutics. Surg Neurol Int. 2014;5:64. http://dx.doi.org/10.4103/2152-7806.132138

20. Sturm D, Bender S, Jones DT, Lichter P, Grill J, Becher O, et al. Pediatric and adult glioblastoma: Multiform (epi)genetic culprits emerge. Nat Rev Cancer. 2014;14(2):92–107. http://dx.doi.org/10.1038/nrc3655

21. Engelhard HH, Villano JL, Porter KR, Stewart AK, Barua M, Barker FG, et al. Clinical presentation, histology, and treatment in 430 patients with primary tumors of the spinal cord, spinal meninges, or cauda equine. J Neurosurg Spine. 2010;13:67–77. http://dx.doi.org/10.3171/2010.3.SPINE09430

22. Adams H, Chaichana KL, Avendano J, Liu B, Raza SM, Quinones-Hinojosa A. Adult cerebellar glioblastoma: Understanding survival and prognostic factors using a population-based database from 1973–2009. World Neurosurg. 2013;80(6):e181–3. http://dx.doi.org/10.1016/j.wneu.2013.02.010

23. Babu R, Sharma R, Karikari IO, Owens TR, Friedman AH, Adamson C. Outcome and prognostic factors in adult cerebellar glioblastoma. J Clin Neurosci. 2013;20:1117–21. http://dx.doi.org/10.1016/j.jocn.2012.12.006

24. Jeswani S, Nuno M, Folkerts V, Mukherjee D, Black KL, Patil CG. Comparison of survival between cerebellar and supratentorial glioblastoma patients: Surveillance, epidemiology, and end results (SEER) analysis. Neurosurgery. 2013;73:240–6. http://dx.doi.org/10.1227/01.NEU.0000430288.85680.37

25. Konar SK, Maiti TK, Bir SC, Kalakoti P, Bollam P, Nanda A. Predictive factors determining the overall outcome of primary spinal glioblastoma multiforme: An integrative survival analysis. World Neurosurg. 2016;86:341–8. http://dx.doi.org/10.1016/j.wneu.2015.08.078

26. Jiang L, Fang X, Bao Y, Zhou YJ, Chen XY, Ding MH, et al. Association between the XRCC1 polymorphisms and glioma risk: A meta-analysis of case-control studies. PLoS One. 2013;8(1):e55597. http://dx.doi.org/10.1371/journal.pone.0055597

27. Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, et al. The molecular basis of Turcot’s syndrome. N Engl J Med. 1995 Mar 30;332(13):839–47. http://dx.doi.org/10.1056/NEJM199503303321302

28. Kretz D, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M, et al. German glioma network long-term survival with glioblastoma multiforme. Brain. 2007;130(10):596–606. http://dx.doi.org/10.1093/brain/awm204

29. Wang R, Chadalavada K, Wilshire J, Kowalik U, Hovinga KE, Fligelman B, et al. Glioblastoma stem-like cells give rise to tumor endothelium. Nature. 2010;468:829–3. http://dx.doi.org/10.1038/nature09624

30. Dirks PB. Brain tumor stem cells: Bringing order to the chaos of brain cancer. J Clin Oncol. 2008;26:2916–24. http://dx.doi.org/10.1200/JCO.2008.17.6792

31. Chen J, McKay RM, Parada LF. Malignant glioma: Lessons from genomics, mouse models, and stem cells. Cell. 2012;149:36–47. http://dx.doi.org/10.1016/j.cell.2012.03.009

32. Pollard SM, Yoshikawa K, Clarke ID, Danovi D, Stricker S, Russell R, et al. Glioma stem cell lines expanded in adherent culture have tumor-specific phenotypes and are suitable for chemical and genetic screens. Cell Stem Cell. 2009;4:568–80. http://dx.doi.org/10.1016/j.stem.2009.03.014
33. Ohgaki H, Kleihues P. The definition of primary and secondary glioblastoma. Clin Cancer Res. 2013;19:764–72. http://dx.doi.org/10.1158/1078-0432.CCR-12-3002
34. Fueyo J, Alemany R, Gomez-Manzano C, Fuller GN, Khan A, Conrad CA, et al. Preclinical characterization of the antiglioma activity of a tropism-enhanced adenovirus targeted to the retinoblastoma pathway. J Natl Cancer Inst. 2003;95:652–60. http://dx.doi.org/10.1093/jnci/djg159.9.652
35. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRα, IDH1, EGFR, and NF1. Cancer Cell. 2010;17:98–10. http://dx.doi.org/10.1016/j.ccr.2009.12.020
36. Arjona D, Rey JA, Taylor SM. Early genetic changes involved in low-grade astrocytic tumor development. Curr Mol Med. 2006;6:645–50. http://dx.doi.org/10.2174/156652406778195017
37. Furnari FB, Fenton T, Bachoo RM, Mukasa A, Stommel JM, Stegh A, et al. Malignant astrocyticglioma: Genetics, biology, and paths to treatment. Genes Dev. 2007;21:683–710. http://dx.doi.org/10.1101/gad.1596707
38. Nakamura M, Yang F, Fujisawa H, Yonekawa Y, Kleihues P, Ohgaki H. Loss of heterozygosity on chromosome 19 in secondary glioblastomas. J Neuropathol Exp Neurol. 2000;59:539–43. http://dx.doi.org/10.1093/jnen/59.6.539
39. Watanabe K, Tachibana O, Sata K, Yonekawa Y, Kleihues P, Ohgaki H. Overexpression of the EGF receptor and p53 mutations are mutually exclusive in the evolution of primary and secondary glioblastomas. Brain Pathol. 1996;6:217–23. http://dx.doi.org/10.1111/j.1460-9526.1996.tb00848.x
40. Dillman RO, Duma CM, Schiltz PM, DePriest C, Ellis RA, Okamoto K, et al. Intracavitary placement of autologous lymphokine-activated killer (LAK) cells after resection of recurrent glioblastoma. J Immunother. 2004;27:398–404. http://dx.doi.org/10.1097/01002371-200409000-00009
41. Watanabe T, Nobusawa S, Kleihues P, Ohgaki H. IDH1 mutations are early events in the development of astrocytomas and oligodendrogliomas. Am J Pathol. 2009;174:1149–53. http://dx.doi.org/10.2353/ajpath.2009.080958
42. Phillips HS, Khambandha S, Chen R, Forrest WF, Soriano RH, Wu TD, et al. Molecular subclasses of high grad glioma predict prognosis, delineate a patterns of disease progression and resemble stages in neurogenesis. Cancer Cell. 2006;9:157–73. http://dx.doi.org/10.1016/j.ccr.2006.02.019
43. Murat A, Migliavacca E, Gorlia T, Lambiv WL, Shay T, Hamou MF, et al. Stem cell-related “self-renewal” signature and high epidermal growth factor receptor expression associated with resistance to concomitant chemo radiotherapy in glioblastoma. J Clin Oncol. 2008;26:3015–24. http://dx.doi.org/10.1200/JCO.2007.15.7164
44. Brennan C, Momota H, Hambardzumyan D, Ozawa T, Tandon A, Pedraza A, et al. Glioblastoma sub-classes can be defined by activity among signal transduction pathways and associated genomic alterations. PLoS One. 2009;4:e7752. http://dx.doi.org/10.1371/journal.pone.0007752
45. Reuss DE, Kratz A, Sahm F, Capper D, Schrimpf D, Koelsche C, et al. Adult IDH wild type astrocytomas biologically and clinically resolve into other tumor entities. Acta Neuropathol. 2015;130(3):407–17. http://dx.doi.org/10.1007/s00401-015-1454-8
46. Perry A, Miller CR, Gujrati M, Scheithauer BW, Zambrano SC, Jos SC, et al. Malignant gliomas with primitive neuroectodermal tumor-like components: A clinicopathologic and genetic study of 53 cases. Brain Pathol. 2009;19:81–90. http://dx.doi.org/10.1111/j.1750-3639.2008.00167.x
47. Joseph NM, Phillips J, Daihya S, Felicella M, Tihan T, Bra DJ, et al. Diagnostic implications of IDH1-R132H and OLIG2 expression patterns in rare and challenging glioblastoma variants. Mod Pathol. 2013;26:315–26. http://dx.doi.org/10.1038/modpathol.2012.173
48. Wrensch W, Fisher JL, Schwartzbaum A, Bondy M, Berger M, Aldape KD. Molecular epidemiology of gliomas in adults. Neurosurgical Focus. 2005;19(5):1–11. http://dx.doi.org/10.3171/foc.2005.19.5.6
49. Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of Glioblastoma multiforme. Nat Clin Pract Neurol. 2006;2:494–503. http://dx.doi.org/10.1038/ncpneuro0289
50. Brenner AV, Butler MA, Wang SS, Ruder AM, Rothman N, Schulte PA, et al. Single-nucleotide polymorphisms in selected cytokine genes and risk of adult glioma Carcinogenesis. 2007;28(12):2543–47. http://dx.doi.org/10.1093/carcin/bgm210
51. Lachance DH, Yang P, Johnson DR, Decker PA, Kollmeyer TM, McCoy LS, et al. Associations of high-grade glioma with glioma risk alleles and histories of allergy and smoking. Am J Epidemiol. 2011;174(5):574–81. http://dx.doi.org/10.1093/aje/kwr124

52. Scheurer ME, Amirian S, Davlin TL, Rice T, Wrensch M, Bondy ML. Effects of antihistamine and anti-inflammatory medication use on risk of specific glioma histologies. Int J Cancer. 2011;129(9):2290–6. http://dx.doi.org/10.1002/ijc.25883

53. Fujita M, Kohanbash G, Fellows-Mayle W, Hamilton RL, Komohara Y, Decker SA, et al. COX-2 blockade suppresses gliomagenesis by inhibiting myeloid-derived suppressor cells. Cancer Res. 2011;71(7):2664–74. http://dx.doi.org/10.1158/0008-5472.CAN-10-3055

54. Seliger C, Meier CR, Becker C, Jick SS, Bogdahn U, Hau P, et al. Use of selective cyclooxygenase-2 inhibitors, other analgesics, and risk of glioma. PLoS One. 2016;11(2):1–12. http://dx.doi.org/10.1371/journal.pone.0149293

55. Kitahara CM, Wang SS, Melin BS, Wang Z, Braganza M, Albanes D, et al. Association between adult height, genetic susceptibility and risk of glioma. Int J Epidemiol. 2012 Aug;41(4):1075–85. http://dx.doi.org/10.1093/ije/dys114

56. Hoschberg F, Toniolo P, Cole P, Scalcman M. Nonoccupational risk indicators of glioblastoma in adults. J Neurooncol. 1999;8:55–60.

57. Deltour I, Auvinen A, Feychting M, Johansen C, Klaeboe L, Sankila R, et al. Mobile phone use and incidence of glioma in the Nordic countries 1979–2008: Consistency check. Epidemiology. 2012;23(2):301–7. http://dx.doi.org/10.1097/EDE.0b013e3182448295

58. Benson VS, Pirie K, Schuz J, Reeves GK, Beral V, Green J. Mobil phone use and risk of brain neoplasms and other cancers: Prospective study. Int J Epidemiol. 2013;43(3):792–802. http://dx.doi.org/10.1093/ije/dyt072

59. Nieder C, Grosu A, Astner S, Molls M. Treatment of unresectable glioblastoma multiforme. Anticancer Res. 2005;25(12):4605–10.

60. Malmöstrom A, Gronberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide versus standard 6-week radiotherapy versus hypo fractionates radiotherapy in patients older than 60 years with glioblastoma. The Nordic randomized phase 3 trial. Lancet Oncol. 2012;13:916–26. http://dx.doi.org/10.1016/S1470-2045(12)70265-6

61. Stummer W, Reulen H-J, Meinel T, Pichlmeyer U, Schummer W, Tonn J, et al. Extent of resection and survival in glioblastoma multiforme: Identification of and adjustment for bias. Neurosurgery. 2008;62(3):564–76. http://dx.doi.org/10.1227/01.neu.0000317304.31579.17