8 Epidemiology and Outcome of Glioblastoma

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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

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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).

TABLE 1 **Age-adjusted Incidence per 100,000 Persons (ICD-O Morphology Code 9450) in Different Countries**

Region	Years	Overall	Ref
United States	2006–2010	3.19	2
Australia	2000–2008	3.40	13
England	1999–2003	2.05	14
Korea	2005	0.59	15
Greece	2005–2007	3.69	17
Jordan	2012–2013	0.89	16

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).

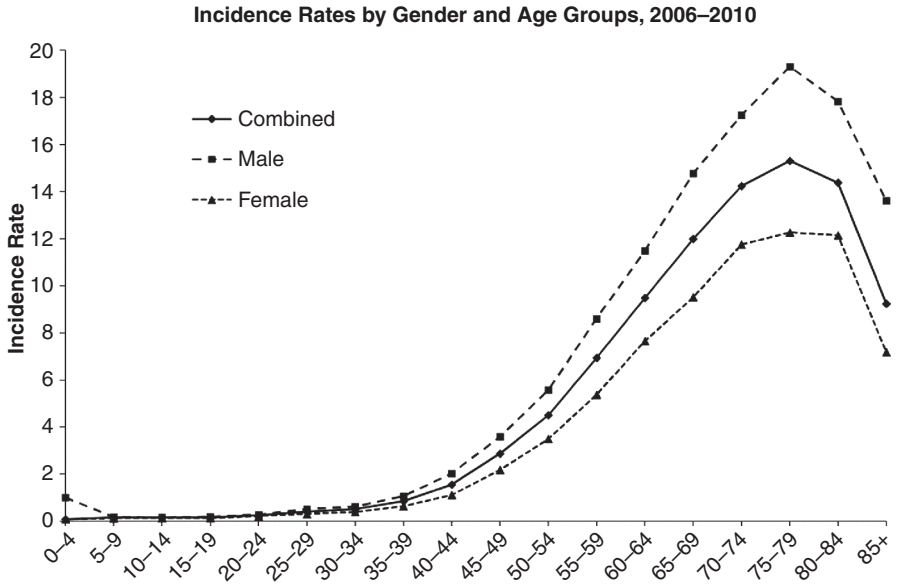

Figure 1 Age-adjusted and age-specific incidence rates for glioblastoma at diagnosis and gender, CBTRUS statistical report: NPCR and SEER, 2006–2010. X-axis, age groups; Y-axis, incidence rates. Rates are per 100,000 and age-adjusted to the 2000 US standard population. NPCR, CDC's National Program of Cancer Registries; SEER, NCI's Surveillance, Epidemiology, and End Results program. (Adapted from Ref. (11).)

ETHNICITY 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.

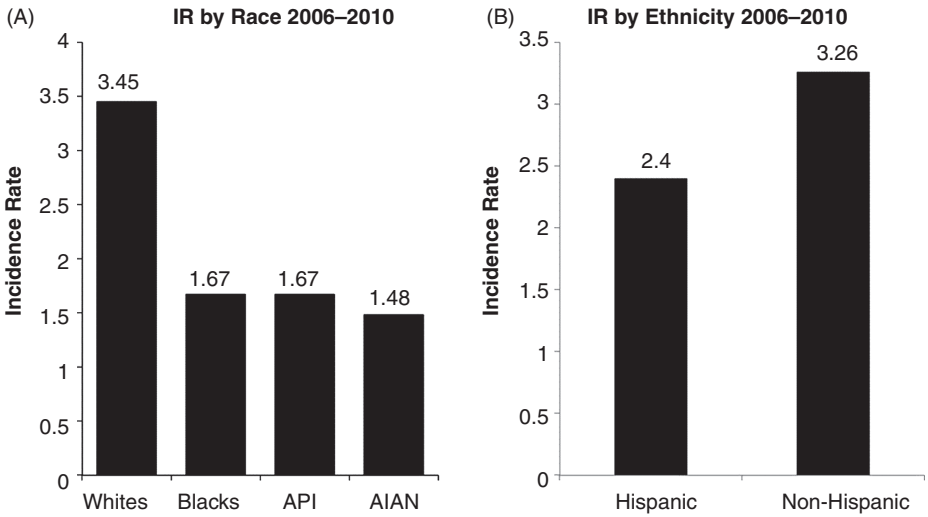

Figure 2 (A) Average annual age-adjusted incidence rates of glioblastoma by race, CBTRUS statistical report: NPCR and SEER, 2006 to 2010. X-axis, race; Y-axis, incidence rates. (B) Average annual age-adjusted incidence rates of glioblastoma by ethnicity, CBTRUS statistical report: NPCR and SEER, 2006 to 2010. X-axis, ethnicity; Y-axis, incidence rates. Rates are per 100,000. AIAN, Asian Indian Alaskan Native. (Adapted from Ref. (11).)

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 IHD1. 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 indefinitive 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.

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