Brain Tumors

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1.1 General Findings

Primary brain tumors refer to a heterogeneous group of tumors arising from cells within the CNS. Meningiomas are the most common nonmalignant primary brain tumors, followed by pituitary and nerve sheath tumors. Gliomas represent 75% of malignant primary brain tumors in adults and of these, more than half are glioblastomas. Gliomas are tumors of neuroectodermal origin arising from glial or precursor cells [1].

Although CNS tumors are rare, they are a significant cause of cancer morbidity and mortality, especially in children and young adults where they respectively account for approximately 30% and 20% of cancer deaths. They are also a cause of excessive mortality relative to other cancers [2].

1.2 Classification

Classification of central nervous system (CNS) tumors has always been a critical component of the epidemiologic, clinical, and basic-level understanding of this type of neoplasms. Historically, brain tumor classification was exclusively carried out based on histomorphologic features, of tumors, an approach compatible within the capabilities of most clinical centers throughout the world and primarily dependent on light microscopic features in hematoxylin and eosin-stained sections.

Advances in the molecular understanding of brain tumors that have occurred since 2007 have driven the concept that incorporation of clinically relevant molecular markers can provide a biologic basis for classification, that, when integrated with morphologic features, may result in a classification that promotes increased accuracy and precision.

As a result, the recent 2016 update of the WHO Classification of Tumors of the Central Nervous System (2016 CNS WHO) represents a revolutionary shift from previous iterations by having, for the first time, tumor classes defined not only by their histomorphologic features, but also by key diagnostic molecular parameters.

The 2016 CNS WHO officially represents an update of the 2007 fourth Edition rather than a formal fifth Edition. The use of "integrated" phenotypic and genotypic parameters for CNS tumor classification adds a level of objectivity that has been missing from some aspects of the diagnostic process in the past. This new characterization has primarily involved gliomas that are further classified according to WHO grading [3, 4].

1.3 2016 World Health Organization Classification of Tumors of the Central Nervous System

Diffuse Astrocytic and Oligodendroglial Tumors

WHO grade II

Diffuse astrocytoma IDH-mutant—9400/3

– Gemistocytic astrocytoma IDH-mutant—9411/3

Diffuse astrocytoma IDH-wildtype—9400/3

Diffuse astrocytoma NOS—9400/3

Oligoastrocytoma NOS—9382/3

Oligodendroglioma IDH-mutant, 1p19q co-deleted—9450/3

Oligodendroglioma NOS

WHO grade III

Anaplastic astrocytoma IDH-mutant—9401/3

Anaplastic astrocytoma IDH-wildtype—9401/3

Anaplastic astrocytoma NOS 9401/3

Anaplastic oligoastrocytoma NOS—9382/3

Anaplastic oligodendroglioma IDH-mutant, 1p19q co-deleted—9451/3

Anaplastic oligodendroglioma NOS

WHO grade IV

Glioblastoma IDH wildtype—9440/3

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– Giant cell glioblastoma—9441/3
– Gliosarcoma 9442/3
– *Epithelioid glioblastoma—9440/3*

Glioblastoma IDH-mutant—9440/3∗
Glioblastoma NOS—9440/3
Diffuse midline glioma, H3K27M-mutant—9385/3∗

Other Astrocytic Tumors
Pilocytic astrocytoma—9421/1

– Pilomixoid astrocytoma—9425/3

Subependymal giant cell astrocytoma—9384/1
Pleomorphic xanthoastrocytoma—9424/3
Anaplastic pleomorphic xanthoastrocytoma 9424/3

Ependymal Tumors
WHO grade I
Subependymoma—9383/1
Myxopapillary ependymoma—9394/1
WHO grade II
Ependymoma—9391/3

– Papillary ependymoma—9393/3
– Clear cell ependymoma—9391/3
– Tanycytic ependymoma—9391/3

Ependymoma RELA fusion-positive—9396/3 ∗
WHO grade III
Anaplastic ependymoma—9392/3

Other Gliomas
Angiocentric glioma—9431/1
Chordoid glioma of the third ventricle—9444/1
Astroblastoma—9430/3

Choroid Plexus Tumors
Choroid plexus papilloma—9390/0
Atypical choroid plexus papilloma—9390/1
Choroid plexus carcinoma—9390/3

Neuronal and Mixed Neuronal-Glial Tumors
Dysembryoplastic neuroepithelial tumor—9413/0
Gangliocytoma—9492/0
Ganglioglioma—9505/1
Anaplastic ganglioglioma—9505/3
Dysplastic gangliocytoma of the cerebellum—(Lhermitte-Duclos)—9493/0
Desmoplastic infantile astrocytoma and ganglioglioma—9412/1
Papillary glioneuronal tumor—9509/1
Rosette-forming glioneuronal tumor of the fourth ventricle—9509/1
Diffuse leptomeningeal glioneuronal tumor—no IDC-O code
Central neurocytoma—9506/1
Extraventricular neurocytoma—9506/1
Cerebellar liponeurocytoma—9506/1
Paraganglioma—8680/1

Tumors of the Pineal Region
Pineocytoma—9361/1
Pineal parenchymal tumor of intermediate differentiation—9362/3
Pineoblastoma—9362/3
Papillary tumor of the pineal region—9395/3

Embryonal Tumors
Medulloblastoma genetically defined

– WNT-activated—9475/3 ∗
– SHH-activated & TP53-mutant—9476/3
– SHH-activated & TP53-wildtype—9471/3
– *Group 3—9477/3*
– *Group 4—9477/3*

Medulloblastoma histologically defined

– Classic—9470/3
– Desmoplastic/nodular—9471/3
– Extensive nodularity—9471/3
– Large cell/anaplastic—9470/3.

Medulloblastoma NOS—9470/3
Embryonal tumors with multilayered rosettes C19MC altered—9478/3 ∗
Embryonal tumors with multilayered rosettes NOS 9478/3 ∗
Medulloepithelioma 9501/3
CNS neuroblastoma 9500/3
CNS ganglioneuroblastoma 9490/3
CNS embryonal tumor, NOS 9473/3
Atypical teratoid/rhabdoid tumor 9508/3
CNS embryonal tumor with rhabdoid features 9508/3

Tumors of Cranial and Paraspinal Nerves
Schwannoma (neurilemoma, neurinoma)—9560/0

– Cellular schwannoma—9560/0
– Plexiform schwannoma—9560/0
– Melanotic schwannoma—9560/1
– Neurofibroma—9540/0
– Atypical neurofibroma—9540/0
– Plexiform neurofibroma—9550/0

Perineurioma 9571/0
Malignant peripheral nerve sheath tumor (MPNST)—9540/3

– Epithelioid—9540/3
– With perineural differentiation 9540/3

Meningiomas
Meningioma—9530/0
Meningothelial meningioma—9531/0
Fibrous meningioma—9532/0
Transitional meningioma—9537/0
Psammomatous meningioma—9533/0
Angiomatous meningioma—9534/0
Microcystic meningioma—9530/0
Secretory meningioma—9530/0
Lymphoplasmacyte-rich meningioma—9530/0
Metaplastic meningioma—9530/0
Chordoid meningioma—9538/1
Clear cell meningioma—9538/1
Atypical meningioma—9539/1
Papillary meningioma—9538/3
Rhabdoid meningioma—9538/3
Anaplastic meningioma (malignant)—9530/3

Mesenchymal, Non-meningothelial Tumors
Solitary fibrous tumor of the dura/hemangiopericytoma

– Grade 1—8815/0
– Grade 2—8815/1
– Grade 3—8815/3

Hemangioblastoma—9161/1
Hemangioma—9120/0
Epithelioid hemangioendothelioma—9133/3
Angiosarcoma—9120/3
Kaposi sarcoma—9140/3
Ewing sarcoma / PNET—9364/3
Lipoma—8850/0
Angiolipoma—8861/0
Liposarcoma—8850/3
Desmoid-type fibromatosis—8821/1
Myofibroblastoma—8825/0
Inflammatory myofibroblastic tumor—8825/1
Benign fibrous histiocytoma—8830/0
Fibrosarcoma—8810/3
Undifferentiated pleomorphic sarcoma / malignant fibrous histiocytoma—8830/3
Leiomyoma—8890/0
Leiomyosarcoma—8890/3
Rhabdomyoma—8900/0
Rhabdomyosarcoma—8900/3
Chondroma—9220/0
Chondrosarcoma—9220/3
Osteoma 9180/0
Osteochondroma—9210/0
Osteosarcoma—9180/3

Melanocytic Tumors
Meningeal melanocytosis—8728/0
Meningeal melanocytoma—8728/1
Meningeal melanomatosis—8728/3
Meningeal melanoma—8720/3

Lymphomas
Diffuse large B-cell lymphoma of the CNS—9680/3
Immunodeficiency-associated CNS lymphomas

– AIDS-related diffuse large B-cell lymphoma
– EBV-positive diffuse large B-cell lymphoma, NOS
– lymphomatoid granulomatosis—9766/1

Intravascular large B-cell lymphoma—9712/3
Low-grade B-cell lymphomas of the CNS
T-cell and NK/T-cell lymphomas of the CNS
Anaplastic large cell lymphoma

– ALK-positive—9714/3
– ALK-negative—9702/3

MALT lymphoma of the dura—9699/3

Histiocytic Tumors
Langerhans cell histiocytosis—9751/3
Erdheim-Chester disease—9750/1
Rosai-Dorfman disease
Juvenile xanthogranuloma
Histiocytic sarcoma—9755/3

Germ Cell Tumors
Germinoma—9064/3
Embryonal carcinoma—9070/3
Yolk sac tumor—9071/3
Choriocarcinoma—9100/3
Teratoma

– Mature—9080/0
– Immature—9080/3
– With malignant transformation—9084/3
Mixed germ cell tumors—9085/3

Tumors of the Sellar Region

Craniopharyngioma—9350/1

- Adamantinomatous—9351/1
- Papillary—9352/1

Granular cell tumor of the sellar region—9582/0
Pituicytoma—9432/1
Spindle cell oncocytoma—8291/0

Metastatic Tumors

Notes: ***NOS****: not otherwise specified.is from the International Classification of Disease for Oncology (ICD-O).*

Four-digit code: *is from the International Classification of Disease for Oncology (ICD-O).*

/: the number after the slash (/) refers to biological behavior, not WHO Grade.

**: refers to a 'new' tumor in the classification.*

Italics*: refers to a provisional inclusion.*

CNS tumor diagnoses should consist of a histopathological name followed by the genetic features as adjectives, as *Diffuse astrocytoma IDH-mutant or Oligodendroglioma IDH-mutant and 1p/19q-codeleted.*

For a tumor lacking a genetic mutation, the term *wild-type* can be used if an official "wildtype" entity exists: ex. *Glioblastoma, IDH-wildtype*. However, it should be pointed out that in most such situations, a formal *wildtype* diagnosis is not available, and a tumor lacking a diagnostic mutation is given an NOS designation.

In other words, NOS does not define a specific entity; rather it designates a group of lesions that cannot be classified into any of the defined groups (insufficient information, not tested) [4]**.**

1.4 Molecular Markers

The most common markers used to characterize gliomas according to the new classification are listed below [1, 5].

IDH: Isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) mutations are thought to be an early event of gliomagenesis, and are more commonly found in lower-grade gliomas (>70% grades II–III astrocytomas; 100% oligodendrogliomas) than in glioblastomas, of which only 10% are referred to as secondary glioblastoma (defined when arising from a lower grade astrocytoma) or glioblastoma IDH-mutant (defined molecularly). Diffuse gliomas harboring IDH1/2 mutations are associated with a better prognosis than diffuse gliomas, IDH-wildtype.

1p/19q: Codeletion of chromosomes 1p and 19q results from a non-balanced centromeric translocation. This codeletion, combined with *IDH* mutation, is now required for the diagnosis of oligodendroglioma *IDH*-mutant and 1p/19q codeleted. 1p/19q codeletion confers a favorable prognosis among diffuse gliomas and is predictive of an increased response to alkylating chemotherapy.

H3 Lys27Met: Mutations in the genes encoding histone proteins H3.3 or H3.1 resulting in lysine to methionine substitution at amino acid 27 (Lys27Met or K27 M) molecularly defines the novel entity of diffuse midline glioma H3 Lys27Met-mutant, WHO grade IV.

H3 Lys27Met mutation is mutually exclusive with *IDH* mutation, and has been suggested to be an early event of gliomagenesis. Among all diffuse gliomas, and within diffuse midline gliomas in general, the H3 Lys27Met-mutant tumors portend the worst prognosis (2-year survival <10%). They are considered WHO grade IV even if their histology otherwise appears low-grade or anaplastic.

MGMT: O^6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair protein involved in repairing the damage that has been induced by alkylating agents such as temozolomide. Methylation of the *MGMT* promoter (MGMTp) silences the *MGMT* gene and reduces the ability of tumor cells to repair such damage. MGMTp methylation predicts benefit from alkylating chemotherapies in glioblastoma patients, including elderly patients. MGMTp methylation also confers a favorable prognosis to both anaplastic astrocytomas and glioblastomas. MGMTp methylation is common in glioblastomas (30–50% of primary IDH-wildtype, glioblastoma) and in oligodendrogliomas (>90%), but less common in lower grade astrocytomas.

BRAF: B-raf is a protein kinase regulating the RAS-RAFMEK- ERK cellular signaling pathway. *BRAF* alterations, such as BRAF V600E mutation or KIAA1549-BRAF fusion, activate that pathway, and ultimately result in tumor growth and maintenance. BRAF V600E mutation is most commonly found in circumscribed gliomas, such as pleomorphic xanthoastrocytoma (60–80%), dysembryoplastic neuroepithelial tumors (30%), gangliogliomas (25%), and pilocytic astrocytomas (5–15%), but can also be found in about half of IDH-wildtype epithelioid glioblastomas. KIAA1549-BRAF fusion is almost exclusive to pilocytic astrocytomas, found in about 75% of those, and predict an indolent course.

C11orf95-RELA gene fusion: surrogate IHC (immunohistochemistry) marker to identify high-risk supratentorial RELA-fusion-positive ependymoma. No specific targeted therapy is related.

Additional markers although currently not required for diagnosis [5] may be helpful in supporting the morphological diagnosis and also provide prognostic and predictive information they can affect decision-making in the management of high-grade glioma. Moreover these markers include:

alpha-thalassemia/mental retardation syndrome Xlinked (ATRX) expression; *mutations in the tumor protein 53 (TP53) gene*; *mutations in the telomerase reverse transcriptase (TERT) promoter:* indicates poor prognosis and may guide more aggressive intervention; *combined chromosome 7gain*

and chromosome 10q loss (7þ10qe): indicate a more aggressive tumor paralleling a glioblastoma; *epidermal growth factor receptor (EGFR) amplification.*

1.5 Commentary

In the new 2016 classification, gliomas are separated into circumscribed gliomas (WHO grade I) and diffusely infiltrating gliomas (WHO grades II–IV; whether astrocytic or oligodendroglial) based on their pattern of growth and the presence or not of *IDH* mutation.

1.5.1 Circumscribed Gliomas

Circumscribed gliomas represent tumors mostly regarded as benign and curable by complete resection. Circumscribed gliomas do not have an *IDH* mutation and have frequent *BRAF* mutations and fusions (e.g., pilocytic astrocytoma and pleomorphic xanthoastrocytoma) [1].

1.5.2 Diffuse Infiltrating Gliomas

Diffuse gliomas are almost never cured by resection alone, are graded using histopathological criteria, and are now classified according to diagnostic molecular markers (presence or not of IDH mutation). In this new classification, the diffuse gliomas include the WHO grade II and III astrocytic tumors, the grade II and III oligodendrogliomas, and the grade IV glioblastomas.
Histologically, grade II (low grade) diffuse astrocytomas show nuclear atypia, grade III (anaplastic) display increased mitotic activity, and grade IV (glioblastomas) show additional microvascular proliferation, necrosis, or both [1].

1.5.3 Astrocytoma/Oligodendgroglioma

Gliomas wearing discriminating *IDH* gene alteration with *TP53* and *ATRX* mutations are called diffuse astrocytoma (WHO grade II) or anaplastic (WHO grade III) according to histological features and behavior; these tumors are thus distinguished from oligodendroglioma by the presence of intact 1p19q.

In grade II–III gliomas with *IDH*1 mutation but no *ATRX* mutation, 1p/19q codeletion status assessment in fact is required to distinguish astrocytomas from oligodendrogliomas [1].

Astrocytic tumors are classified as either IDH-mutant or IDH-wildtype, separating these tumors into two prognostic groups. Retrospective assessment of the IDH mutation status in patients from historical clinical trials confirms the marked separation of outcome between IDH-mutant and IDH-wildtype tumors with a median survival of 9.4 and 1.3 years in IDH-mutant and IDH-wildtype tumors, respectively [5], so the presence of IDH mutation is an index of better prognosis.

The diagnosis of oligodendroglioma hence requires the demonstration of IDH mutation and 1p/19q codeletion, as its correct definition including histological and molecular characteristics is: *diffusely infiltrating*, *slow-growing glioma with IDH1 or IDH2 mutation and codeletion of chromosomal arms 1p and 19q* in which microcalcifications and a delicate branching capillary network are typical, findings that however are highly characteristic of the entity, but not necessary for the diagnosis. These tumors are graded as oligodendroglioma (WHO grade II) or anaplastic oligodendroglioma (WHO grade III).

In the absence of molecular testing or in case of inconclusive genetic results, a histologically typical oligodendroglioma should be diagnosed as NOS.

In pediatric patients, tumors with classical morphological features of oligodendroglioma frequently lack IDH mutations and 1p19q co-deletion. After histological mimics are excluded, these tumors can be classified as oligodendroglioma lacking IDH mutation and 1p/19q co-deletion (pediatric-type oligodendroglioma).

Two diffuse astrocytoma variants have been deleted from the WHO classification: *protoplasmic astrocytoma* and *fibrillary astrocytoma.* Only *gemistocytic astrocytoma* remains as a distinct variant of diffuse astrocytoma, IDH-mutant.

Gliomatosis cerebri has also been deleted from the 2016 CNS WHO classification as a distinct entity, rather being considered a growth pattern found in many gliomas, including IDH-mutant astrocytic and oligodendroglial tumors as well as IDH-wildtype glioblastomas.

Currently, most diagnosis of oligoastrocytoma, using both genotype (IDH mutation and 1p/19q codeletion status) and phenotype features, results being compatible with either an astrocytoma or oligodendroglioma, remaining only rare reports of molecularly "true" oligoastrocytomas consisting of histologically and genetically distinct astrocytic (IDH-mutant, *ATRX*-mutant, 1p/19q-intact) and oligodendroglial (IDH-mutant, *ATRX*-wildtype and 1p/19q-codeleted) tumor populations coexisting in the same pathological tissue.

In the 2016 CNS WHO, therefore, the prior diagnoses of oligoastrocytoma and anaplastic oligoastrocytoma are now designated as NOS categories, since these diagnoses should be rendered only in the absence of diagnostic molecular testing or in the very rare instance of a dual-genotype oligoastrocytoma.

The diagnostic use of both histology and molecular genetic features also raises the possibility of discordant

results, e.g., a diffuse glioma that histologically appears astrocytic but proves to have IDH mutation and 1p/19q codeletion, or a tumor that resembles oligodendroglioma by light microscopy but has IDH, *ATRX,* and *TP53* mutations in the setting of intact 1p and 19q. Notably, in each of these situations, the genotype trumps the histological phenotype, necessitating a diagnosis of *oligodendroglioma, IDH-mutant* and *1p/19q-codeleted* in the first instance and *diffuse astrocytoma, IDH-mutant* in the second [4].

1.5.4 Glioblastoma

Glioblastomas are divided into *glioblastoma IDH-wildtype* (about 90% of cases), which corresponds most frequently with the clinically defined primary or de novo glioblastoma and predominates in patients over 55 years of age; *glioblastoma IDH-mutant* (about 10% of cases), which corresponds closely to so-called secondary glioblastoma with a history of prior lower grade diffuse glioma and preferentially arises in younger patients; *glioblastoma NOS*, a diagnosis that is reserved for those tumors for which full IDH evaluation cannot be performed.

IDH mutant gliomastomas have an improved median survival: 31 months for IDH-mutant versus 15 months for IDH-wildtype glioblastoma.

Diffuse Midline Glioma, H3 K27-mutant: this is a new addition to the WHO classification and is defined by the presence of a K27 M mutation in histone H3. In most cases, this mutation identifies clinically aggressive, contrast-enhancing WHO grade IV tumors in younger adults, usually within the thalamus or brainstem [4].

1.5.5 Ependymoma

The classification of ependymal tumors has remained essentially unchanged in the revised WHO classification. The 2016 WHO classification also includes a new genetically defined supratentorial ependymoma, predominantly, but not exclusively in children, characterized by a RELA fusion, usually to C11orf95. Compared with supratentorial ependymoma overall, this tumor has a worse prognosis, with the median progression-free survival reported as less than 24 months [5].

1.6 Incidence

Incidence rates of glioma vary significantly by histologic type, age at diagnosis, gender, race, and country. The lack of consistent definition of glioma and various glioma histologic types as well as differences in data collection techniques may cause difficulty in comparing incidence rates from different sources. Overall age-adjusted incidence rates (adjusted to the national population of each respective study) for all gliomas range from 4.67 to 5.73 per 100,000 persons. Age-adjusted incidence of glioblastoma, the most common and most deadly glioma subtype in adults, ranges from 0.59 to 3.69 per 100,000 persons. Anaplastic astrocytoma and glioblastoma increase in incidence with age, peaking in the 75–84 age group. Oligodendrogliomas and oligoastrocytomas are most common in the 35–44 age group. In general, gliomas are more common in men than women, with the exception of pilocytic astrocytoma, which occurs at similar rates in men and women. In the United States, gliomas are more common in non-Hispanic whites than in blacks, Asian/Pacific Islanders, and American Indians/Alaska Natives [6].

Brain cancer incidence is highest in Europe, where its annual age-standardized rate (ASR) is 5.5 per 100,000 persons, followed by North America (5.3 per 100,000 persons), Northern Africa (5.0 per 100,000 persons), Western Asia (5.2 per 100,000 persons), and Australia/New Zealand (5.3 per 100,000 persons). It is the lowest in sub-Saharan Africa (0.8 per 100,000 persons), South-Central Asia (1.8 per 100,000 persons), and Oceania beyond Australia and New Zealand (0.5 per 100,000 persons).

Although there was an apparent increase in brain tumor incidence in the decades between 1970 and 2000, this was deemed due to improvements in detection concomitant with the introduction of MRI in the 1980s. It is thought, therefore, that any change in incidence rates noted during that period is likely to be due to changing classifications of tumors, improved diagnostic accuracy, better reporting, and access to health care.

Many analyses have examined the incidence rates of glioma to assess whether rates are increasing. The results of these have generally shown the incidence of glioma overall and glioma subtypes to be fairly stable over the time periods assessed [2].

1.7 Risk Factors

Ionizing Radiation: can damage DNA by inducing both single and double-strand breaks, and this can induce genetic changes leading to cancer. Exposure to therapeutic doses or high-dose radiation is the most firmly established environmental risk factor for glioma development and genetic characteristics also influence the extent of this risk. Gliomas may present as early as 7–9 years after irradiation. Recently, a group of experts came to the consensus that the lowest dose of X-ray or gamma irradiation, for which there is a significant evidence of increased cancer risk, is about 10–50 mSv. It may be particularly relevant in children, whose brains are still in the process of developing at the time of irradiation [7].

The association between high-dose ionizing radiation and brain tumors is considered established in the brain tumor epidemiology literature, but it is not generally accepted in the radiation science literature. This may stem from several factors as brain is a highly differentiated organ with low mitotic activity, making it radioresistant and a series of limitations in studies currently available [6].

Nonionizing Radiation: Extremely Low-Frequency Magnetic Fields: although little is known about potential biological mechanisms through which ELF may play a role in the risk of glioma development, it is thought that it would likely act in cancer promotion/progression.

Cellular Phones: scientific evidence does not support a significant association between the use of cellular phones and the risk of glioma. Nevertheless, continuous surveillance on what may be the effects deriving from the use of these devices is desirable, especially because of the long exposure period and their use by children and adolescents.

Allergies and Atopic Disease: have been reported to be protective against multiple cancer types, including glioma. It has been suggested that this effect may be due to increased surveillance by the innate immune system in those with allergies, but this potential mechanism has not been definitively proven.

Heritable Genetic Risk Factors: several inherited, monogenic Mendelian cancer syndromes are associated with increased incidence of specific glioma subtypes: neurofibromatosis type 1 (astrocytoma and optic nerve glioma) and 2 (ependymoma), tuberous sclerosis (giant cell astrocytoma), Lynch syndrome (GBM and other gliomas), Li–Fraumeni syndrome (GBM and other gliomas), melanoma-neural system tumor syndrome (all gliomas), and Ollier disease/Maffucci syndrome (all gliomas). These monogenic disorders account for only a small proportion of glioma cases (<5% overall).

A small proportion (about 5–10%) of gliomas occur in familial clusters, where a patient has a family history of such tumor. First-degree relatives of patients with glioma have a twofold increased risk of developing a brain tumor, especially when the patient was diagnosed with the neoplasm at a younger age. Linkage studies within these familial glioma clusters have not definitely identified high-penetrance risk variants [7].

Occupational chemical exposure, pesticides, solvents: there are several studies in the literature that evaluate the correlation of other risk factors with the onset of gliomas, but they are not sufficient to clearly enumerate a substance among the established causes leading to this cancer type.

1.8 Prognostic Factors

Prognostic factors vary considerably by tumor type and grade across all glioma subtypes. Younger age, high performance status, lower tumor grade, and greater extent of resection are favorable prognostic factors for most adult primary brain tumors. Over the past decade, molecular genetic alterations have been recognized as more powerful prognostic and predictive markers than histological appearance alone [1].

1.9 Clinical Presentation

Patients with primary brain tumors can present with focal (i.e., related to a specific location in the brain) or generalized symptoms over days to weeks, or months to years, depending on the speed of growth and location of the tumor. Tumors can also be found by brain imaging that has been done for unrelated purposes. Tumors in some functional areas of the brain will cause more obvious focal neurological deficits than in other areas, and tend to be discovered sooner on imaging. Frontal lobe tumors might cause weakness or dysphasia; parietal lobe tumors might cause numbness, hemineglect, or spatial disorientation; tumors involving the optic radiations anywhere in the temporal, parietal, or occipital lobe might cause visual field defects. Conversely, tumors located in the prefrontal lobe, temporal lobe, or corpus callosum often result in subtler cognitive dysfunctions such as personality changes, mood disorders, and short-term memory deficits. Infratentorial tumors can cause a combination of cranial-nerve palsies, cerebellar dysfunction, and long-tract signs. Brain tumors can also present with generalized symptoms and signs, not specific to one anatomic location. For example, 50–80% of patients might present with seizures, about 30% with headaches, and 15% with symptoms of increased intracranial pressure, such as progressive headaches worse at night, morning nausea and vomiting, drowsiness, blurred vision from papilloedema, and horizontal diplopia from cranial nerve VI palsy [1].

1.10 Diagnostic Investigations

In a patient with a suspected brain tumor, MRI with gadolinium is the investigation of choice.

In many cases, this suspicion derives from pathological findings highlighted in the CT scan to which the patient has been subjected in the emergency room where he has addressed due to the onset of symptoms of variable severity.

Additionally, multimodal MRI such as diffusion-weighted imaging and diffusion tensor imaging, MR perfusion, and MR spectroscopy are used to better characterize the tumor cellularity, vascularity, and metabolism, respectively, and can help distinguish tumor from non-neoplastic processes, including treatment effect. CNS staging with craniospinal MRI is performed in selected cases. Whenever a brain metastasis is suspected, a systemic cancer screening with a careful clinical examination, and a chest-abdomen CT should be done [1].

1.11 Surgical Management

The initial treatment for most primary brain tumors is maximal safe resection, with goals of achieving an accurate histological diagnosis, establishing the tumor's molecular genotype, improving the quality of life, and increasing survival. Although there are no randomized controlled trials regarding the benefit of the extent of resection, the available evidence suggests that maximal safe resection improves functional status and reduces mortality in both low-grade and high-grade gliomas. The extent of resection is largely dependent on tumor location, surgeon experience, and use of preoperative and intraoperative techniques. In tumors adjacent to eloquent brain regions, extensive safe resection can be achieved with preoperative imaging techniques localizing functional cortical areas and their subcortical pathways via functional MRI and diffusion tensor imaging, respectively, although awake surgery with intraoperative cortical electrode mapping remains the gold standard. Generally, a contrast MRI should be done within 72 h post-surgery to determine the extent of resection and to differentiate the persistence of pathological tissue (postoperative enhancement) from post-surgical scar (late enhancement) [1].

1.12 Medical Management

Seizures are experienced by about two-thirds of glioma patients and require long-term treatment with antiepileptic drugs. For patients who have not had a seizure, routine antiepileptic drug prophylaxis is not recommended, but can be considered for a brief period perioperatively.

Almost all malignant brain tumor patients receive corticosteroids at some point, most commonly for symptomatic peritumoral vasogenic edema. Although there are no standardized guidelines for steroid dose, duration, and taper schedule, dexamethasone is often preferred due to its lack of mineralocorticoid activity and its long half-life (36–54 h). Usual dosing varies between 2 and 16 mg daily depending on symptoms severity, with similar bioavailability orally or intravenously.

Gliomas confer the highest risk for tumor-associated venous thromboembolism of all cancers. Up to 20% of high-grade glioma patients develop symptomatic venous thromboembolism during the perioperative period, and up to 30% at 1 year. Generally, postoperative venous thromboembolism prophylaxis with compression stocking and low-molecular-weight heparin within 12–24 h of surgery is recommended until ambulation, and does not confer increased risk of major bleeding. Prolonged venous thromboembolism prophylaxis over the perioperative period is, however, not advised due to increased intracranial hemorrhage (5% vs. 1%). Treatment of venous thromboembolism with low-molecular-weight heparin is recommended for at least 3–6 months in low-grade glioma, and lifelong in high-grade gliomas [1].

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