

The WHO Classification of Tumors of the Nervous System

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Abstract. The new World Health Organization (WHO) classification of nervous system tumors, published in 2000, emerged from a 1999 international consensus conference of neuropathologists. New entities include chordoid glioma of the third ventricle, cerebellar liponeurocytoma, atypical teratoid/rhabdoid tumor, and perineurioma. Several histological variants were added, including tanycytic ependymoma, large cell medulloblastoma, and rhabdoid meningioma. The WHO grading scheme was updated and, for meningiomas, extensively revised. In recognition of the emerging role of molecular diagnostic approaches to tumor classification, genetic profiles have been emphasized, as in the distinct subtypes of glioblastoma and the already clinically useful 1p and 19q markers for oligodendroglioma and 22q/IN11 for atypical teratoid/rhabdoid tumors. In accord with the new WHO Blue Book series, the actual classification is accompanied by extensive descriptions and illustrations of clinicopathological characteristics of each tumor type, including molecular genetic features, predictive factors, and separate chapters on inherited tumor syndromes. The 2000 WHO classification of nervous system tumors aims at being used and implemented by the neuro-oncology and biomedical research communities worldwide.

The revised World Health Organization (WHO) classification of tumors of the nervous system was published in 2000 (1) and is the first in the new, third Blue Book series, which will cover the entire range of human neoplasms over the next 5 years. The first edition of the classification of nervous system tumors was published in 1979 and took almost a decade to complete (2). The second edition followed in 1993 and was considered a great step forward as it incorporated the advances in classification resulting from the introduction of immunohistochemistry (3, 4).

Scope and Format of the New WHO Classification

The new Blue Book series represents a significant departure from the format of the prior 2 series in that the formal classification schemes with definitions and ICD-O codes are now accompanied by comprehensive chapters describing the clinical, epidemiological, radiological, pathological, biological, and predictive features of each entity. The book contains over 600 illustrations. Its objective is to offer the worldwide medical and biomedical research community a uniform system of classification for human neoplasms, in accordance with the longstanding WHO paradigm that broad agreement on criteria for

the definition and classification of cancer types and a standardized nomenclature are prerequisites for progress in clinical oncology, multicenter therapy trials, and comparative studies in different countries.

During the past decade our knowledge of the genetic basis of human neoplasms has increased greatly and histological classification of neoplasms is now increasingly supplemented by genetic profiling. The new Blue Book on tumors of the nervous system (1) and the digestive system (5) contain a wealth of genetic data, and the recently published volume on leukemias and lymphomas (6) demonstrates that, for many neoplasms, the cytogenetic and molecular genetic profile is often a definitive criterion for classification. It is anticipated that this trend will continue and that the classification and possibly the grading of human neoplasms will increasingly be based on genomic alterations and gene expression patterns in addition to histological criteria. Thus, the new WHO books are timely, consensus-based classifications suitable for pathologists, geneticists, and clinical oncologists alike.

The 2000 WHO classification of nervous system tumors is based on the consensus recommendations of an international WHO Working Group of experts that convened in Lyon in July 1999 (Table 1). The accompanying chapters were contributed by an even larger international group of neuropathologists and geneticists. The editors of the nervous system volume are Paul Kleihues (Lyon, France) and Webster K. Cavenee (San Diego, CA). The third edition series editors are Paul Kleihues and Leslie Sobin (Armed Forces Institute of Pathology, Washington, DC). The publisher is IARC Press at the International Agency for Research on Cancer (IARC) in Lyon, France, a cancer research institute of the World Health Organization.

ICD-O Codes and Link to Epidemiology

Brain tumors amount to less than 2% of all malignant neoplasms and thus constitute a small fraction of the

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overall human cancer burden. However, a significant proportion of central nervous system (CNS) neoplasms affects children: tumors of the nervous system (including retinoblastomas and peripheral neuroblastomas) rank second in incidence after leukemias. In fact, with improvement in the therapy of leukemias, brain tumors are the leading cause of cancer mortality in children. Finally, it is important to point out that they are among the most devastating to patients, since they affect the organ that defines the “self” (7). In this regard it is also important to note that their unique site and nature make brain tumors among the most expensive of all human neoplasms to treat.

In the past, the collection of reliable, population-based data on the incidence and mortality rates of tumors of the nervous system as well the survival of brain tumor patients was impaired by a frequent lack of correlation between histopathological diagnoses and the respective codes of the International Classification of Diseases—Oncology (ICD-O). Cancer registry data depend heavily on whether tumors of the meninges (192.1 and 192.3) are included in addition to neoplasms of the brain (ICD-O location codes 191.0–191.9), spinal cord (192.2), and cranial nerves (192.0). Often, incidence data are only collected for malignant neoplasms (last digit of the ICD-O code /3), thus excluding most meningiomas and, previously, also low-grade astrocytomas (8). Since the diffuse astrocytomas eventually have a fatal outcome, all astrocytic tumors now have the ICD-O extension /3, with the exception of pilocytic astrocytoma and other rare variants. The new edition of the WHO classification contains the codes of the recently published third edition of the International Classification of Disease—Oncology (ICD-O), which closely corresponds to the current histopathological classification and is expected to greatly facilitate epidemiological analyses of nervous system neoplasms (9).

Grading

The WHO grading system has been retained and, in some instances, amended (Table 2). It is important to point out that for most nervous system tumors the WHO grade is really an estimate of malignancy. Only for the diffuse glial tumors, for which a spectrum of progression from low to high grade exists, is the WHO system a true grading system. For the astrocytic tumors it still largely corresponds to the St. Anne/Mayo system (10), with the exception that WHO grade I is reserved for the pilocytic astrocytoma and that a single mitosis is no longer an absolute criterion for distinguishing grade II from grade III. The WHO grading of meningiomas and meningioma variants has been completely revised to incorporate a combination of histologic typing and grading that reflects the likelihood of recurrence and aggressive behavior (Table 3).

TABLE 1
WHO Classification of Tumors of the Nervous System

Tumors of Neuroepithelial Tissue	
Astrocytic tumors	
Diffuse astrocytoma	9400/3 ¹
Fibrillary astrocytoma	9420/3
Protoplasmic astrocytoma	9410/3
Gemistocytic astrocytoma	9411/3
Anaplastic astrocytoma	9401/3
Glioblastoma	9440/3
Giant cell glioblastoma	9441/3
Gliosarcoma	9442/3
Pilocytic astrocytoma	9421/1
Pleomorphic xanthoastrocytoma	9424/3
Subependymal giant cell astrocytoma	9384/1
Oligodendroglial tumors	
Oligodendroglioma	9450/3
Anaplastic oligodendroglioma	9451/3
Mixed gliomas	
Oligoastrocytoma	9382/3
Anaplastic oligoastrocytoma	9382/3
Ependymal tumors	
Ependymoma	9391/3
Cellular	9391/3
Papillary	9393/3
Clear cell	9391/3
Tanycytic	9391/3
Anaplastic ependymoma	9392/3
Myxopapillary ependymoma	9394/1
Subependymoma	9383/1
Choroid plexus tumors	
Choroid plexus papilloma	9390/0
Choroid plexus carcinoma	9390/3
Glial tumors of uncertain origin	
Astroblastoma	9430/3
Gliomatosis cerebri	9381/3
Chordoid glioma of the 3rd ventricle	9444/1
Neuronal and mixed neuronal-glial tumors	
Gangliocytoma	9492/0
Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)	9493/0
Desmoplastic infantile astrocytoma/ganglioglioma	9412/1
Dysembryoplastic neuroepithelial tumor	9413/0
Ganglioglioma	9505/1
Anaplastic ganglioglioma	9505/3
Central neurocytoma	9506/1
Cerebellar liponeurocytoma	9506/1
Paraganglioma of the filum terminale	8680/1
Neuroblastic tumors	
Olfactory neuroblastoma (Aesthesioneuroblastoma)	9522/3
Olfactory neuroepithelioma	9523/3
Neuroblastomas of the adrenal gland and sympathetic nervous system	9500/3
Pineal parenchymal tumors	
Pineocytoma	9361/1
Pineoblastoma	9362/3
Pineal parenchymal tumor of intermediate differentiation	9362/3
Embryonal tumors	
Medulloepithelioma	9501/3
Ependymoblastoma	9392/3
Medulloblastoma	9470/3
Desmoplastic medulloblastoma	9471/3
Large cell medulloblastoma	9474/3

TABLE 1 (Continued)

Medulloblastoma	9472/3
Melanotic medulloblastoma	9470/3
Supratentorial primitive neuroectodermal tumor (PNET)	9473/3
Neuroblastoma	9500/3
Ganglioneuroblastoma	9490/3
Atypical teratoid/rhabdoid tumor	9508/3
Tumors of Peripheral Nerves	
Schwannoma	
(Neurilemmoma, Neurinoma)	9560/0
Cellular	9560/0
Plexiform	9560/0
Melanotic	9560/0
Neurofibroma	9540/0
Plexiform	9550/0
Perineurioma	9571/0
Intraneural perineurioma	9571/0
Soft tissue perineurioma	9571/0
Malignant peripheral nerve sheath tumor (MPNST)	9540/3
Epithelioid	9540/3
MPNST with divergent mesenchymal and/or epithelial differentiation	9540/3
Melanotic	9540/3
Melanotic psammomatous	9540/3
Tumors of the Meninges	
Tumors of meningeothelial cells	
Meningioma	9530/0
Meningothelial	9531/0
Fibrous (fibroblastic)	9532/0
Transitional (mixed)	9537/0
Psammomatous	9533/0
Angiomatous	9534/0
Microcystic	9530/0
Secretory	9530/0
Lymphoplasmacyte-rich	9530/0
Metaplastic	9530/0
Clear cell	9538/1
Chordoid	9538/1
Atypical	9539/1
Papillary	9538/3
Rhabdoid	9538/3
Anaplastic meningioma	9530/3
Mesenchymal, non-meningothelial tumors	
Lipoma	8850/0
Angiolipoma	8861/0
Hibernoma	8880/0
Liposarcoma (intracranial)	8850/3
Solitary fibrous tumor	8815/0
Fibrosarcoma	8810/3
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
Osteosarcoma	9180/3
Osteochondroma	9210/0
Hemangioma	9120/0
Epithelioid hemangioendothelioma	9133/1

TABLE 1 (Continued)

Hemangiopericytoma	9150/1
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Primary melanocytic lesions	
Diffuse melanocytosis	8728/0
Melanocytoma	8728/1
Malignant melanoma	8720/3
Meningeal melanomatosis	8728/3
Tumors of uncertain histogenesis	
Hemangioblastoma	9161/1
Lymphomas and Hemopoietic Neoplasms	
Malignant lymphomas	9590/3
Plasmacytoma	9731/3
Granulocytic sarcoma	9930/3
Germ Cell Tumors	
Germinoma	9064/3
Embryonal carcinoma	9070/3
Yolk sac tumor	9071/3
Choriocarcinoma	9100/3
Teratoma	9080/1
Mature	9080/0
Immature	9080/3
Teratoma 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	9582/0
Metastatic Tumors	

¹ Morphology code of the International Classification of Diseases for Oncology (ICD-O) and the Systematized Nomenclature of Medicine (SNOMED). Behavior is coded /0 for benign tumors, /1 for low or uncertain malignant potential or borderline malignancy, /2 for in situ lesions, and /3 for malignant tumors.

TABLE 2
Overview of Changes in the New Classification

New disease entities	
Chordoid glioma of the third ventricle	WHO grade II
Cerebellar liponeurocytoma	WHO grade I/II
Atypical teratoid/rhabdoid tumour	WHO grade IV
Perineurioma	WHO grade I
New variants	
Tanycytic ependymoma	WHO grade II
Large cell medulloblastoma	WHO grade IV
Rhabdoid meningioma	WHO grade III
Teratoma with malignant transformation	(no WHO grade)
Deletion	
Polar spongioblastoma	

Astrocytic Tumors

Astrocytic brain tumors span a wide range of neoplasms with distinct clinical, histopathological, and genetic features. Molecular genetic data that has been gathered since the prior WHO classification in 1993 suggest

TABLE 3
WHO Grading of Meningiomas

Meningiomas with low risk of recurrence and/or aggressive growth	
Fibrothelial meningioma	WHO grade I
Fibrous/fibroblastic meningioma	WHO grade I
Transitional (mixed) meningioma	WHO grade I
Psammomatous meningioma	WHO grade I
Angiomatous meningioma	WHO grade I
Microcystic meningioma	WHO grade I
Secretory meningioma	WHO grade I
Lymphoplasmacyte-rich meningioma	WHO grade I
Metaplastic meningioma	WHO grade I
Meningiomas with greater risk of recurrence and/or aggressive growth	
Atypical meningioma	WHO grade II
Clear cell meningioma (intracranial)	WHO grade II
Chordoid meningioma	WHO grade II
Rhabdoid meningioma	WHO grade III
Papillary meningioma	WHO grade III
Anaplastic (malignant) meningioma	WHO grade III
Further: Meningiomas of any subtype or grade with high proliferation index and/or brain invasion.	

that individual histologically defined types of astrocytomas are even more diverse at a biological level (1). For instance, the majority of glioblastomas arise without clinical or histological evidence of a less malignant precursor lesion and these lesions have been designated primary glioblastoma. They manifest in older patients (mean age, 55 yr) after a short clinical history of usually less than 3 months. These primary glioblastomas are characterized by *EGFR* amplification (~40% of cases) and/or overexpression (60%), *PTEN* mutations (30%), *p16^{INK4a}* deletion (30%–40%), *MDM2* amplification (<10%) and/or overexpression (50%), and in 50%–80% of cases, loss of heterozygosity (LOH) on the entire chromosome 10. In contrast, secondary glioblastomas develop more slowly by malignant progression from diffuse (WHO grade II) or anaplastic astrocytoma (WHO grade III) and manifest in younger patients (mean age, 40 yr). Secondary glioblastomas contain *TP53* mutations in approximately 60% of cases; more than 90% of these mutations are already present in the preceding diffuse (WHO grade II) or anaplastic astrocytoma (grade III). The pathway to secondary glioblastomas is further characterized by allelic loss of chromosomes 19q and 10q (14). Histopathologically, an unambiguous distinction of these subtypes has remained elusive, but they clearly evolve through different genetic pathways (11–14). It also remains to be shown whether these subtypes differ significantly with respect to prognosis, but it is likely that they will respond differently to specific novel therapies as they are developed (15). As a result, ongoing clinical trials need to incorporate molecular subtyping and future classification schemes will no doubt be based on such differences as well (16).

During the consensus meeting, discussion focussed on 2 practical issues relating to astrocytomas, the first being a terminology question. In the previous WHO classification (4), the term “astrocytoma,” if not otherwise specified, referred to highly differentiated, diffusely infiltrating grade II neoplasms that typically manifest in the cerebral hemispheres of young adults, as well as the entire group of astrocytic neoplasms. The WHO grade II tumors were also sometimes clinically termed “low-grade astrocytoma,” which similarly risked equating these low-grade diffuse malignancies with the biologically more benign pilocytic astrocytomas, a lesion with different age distribution, location, genetics, and growth pattern. The Working Group therefore decided to use the term “diffuse astrocytoma WHO grade II.”

The second issue discussed by the Working Group with regard to the diffuse astrocytomas was the criterion of a single mitosis, which had previously been cited as a distinguishing feature between grade II and grade III. Recently it has been suggested that the presence of a single mitosis in a resection specimen, found after many fields of searching, does not necessarily connote a worse behavior than that of grade II astrocytoma (17). The group expressed the caution that this might not be true for small needle biopsies in which the presence of a single mitosis has been shown to be of prognostic significance (10). The absolute use of a single mitosis to make this distinction was therefore relaxed, although further investigation of this issue is clearly warranted. While it was agreed that high proliferation indices as determined by MIB-1 immunohistochemistry indicate more anaplastic, higher-grade tumors, both interobserver and interinstitutional variability precluded the MIB-1 index as a sole criterion used to distinguish grade II from grade III astrocytomas.

Oligodendroglial Tumors

Oligodendroglial tumors have recently attracted much attention since many anaplastic oligodendrogliomas can be successfully treated with chemotherapy (18). Furthermore, the sensitivity of anaplastic oligodendrogliomas to chemotherapy has been linked to certain tumor-associated genetic alterations, namely allelic loss of the short arm of chromosome 1 or combined LOH on 1p and 19q (19). In addition, 1p loss (or combined 1p and 19q loss) is associated with significantly prolonged patient survival when compared with oligodendrogliomas that lack these alterations (19, 20). Thus, oligodendroglial tumors are the first brain tumors for which molecular genetic analysis promises to become a routine diagnostic procedure for guiding adjuvant therapy and predicting outcome.

The histological criteria for classification and grading of oligodendroglial tumors have not changed dramatically compared to the 1993 WHO classification. The definition of oligodendroglioma (WHO grade II) has been refined

from “a tumor composed predominantly of neoplastic oligodendrocytes” to “a well-differentiated, diffusely infiltrating tumor of adults that is typically located in the cerebral hemispheres and composed predominantly of cells morphologically resembling oligodendroglia.” The new definition thus includes important clinical, biological, and morphological characteristics, but avoids any statement concerning the unresolved issue of oligodendroglioma histogenesis. Anaplastic oligodendroglioma (WHO grade III) is defined as “an oligodendroglioma with focal or diffuse histological features of malignancy and a less favorable prognosis.” Morphological features indicating anaplasia include increased cellularity, marked cytological atypia, high mitotic activity, microvascular proliferation, and necrosis with or without pseudopalisading. It is important to note that the finding of marked microvascular proliferation and/or pseudopalisading necrosis in an oligodendroglial tumor should not prompt a diagnostic shift towards glioblastoma.

The various cell types that may occur in oligodendroglial tumors have also been more carefully delineated. In addition to the typical “honeycomb cells,” oligodendrogliomas may contain so-called minigemistocytes, which are strongly GFAP-positive. GFAP immunoreactivity may also be present in typical oligodendroglial tumor cells (gliofibrillary oligodendrocytes). Further cell types found in rare oligodendrogliomas include mucocytes, signet-ring cells, and eosinophilic granular cells. Some tumors contain areas resembling polar spongioblastoma, i.e. palisaded rows of tumor cells with somewhat elongated nuclei. The histological recognition of any of these cell types or architectures in an oligodendroglioma does not qualify for the diagnosis of oligoastrocytoma (mixed glioma).

Oligoastrocytomas: The histological classification of oligoastrocytoma (WHO grade II) and anaplastic oligoastrocytoma (WHO grade III) is notoriously difficult and controversial. Unfortunately, reliable diagnostic immunohistochemical markers for neoplastic oligodendrocytes are only now becoming available (21). Similarly, no specific molecular genetic alterations separate oligoastrocytomas from diffuse astrocytomas or oligodendrogliomas. The available data indicate that oligoastrocytomas show genetic changes either typical for diffuse astrocytomas, e.g. *TP53* mutation and LOH on 17p, or for oligodendrogliomas, e.g. LOH on 1p and 19q (22, 23). Compared to oligodendrogliomas, the prognostic and/or therapeutic significance of LOH on 1p in oligoastrocytomas is less clear (20, 24).

With respect to histological diagnosis, the WHO Working group has closely adhered to the 1993 WHO classification and defined oligoastrocytoma as “a tumor showing a conspicuous mixture of 2 distinct neoplastic cell types resembling the tumor cells in oligodendroglioma

and diffuse astrocytoma.” The 2 components may be separated into distinct areas or diffusely admixed. However, a quantitative assessment of the individual components is not advocated since in most instances the true extent of each component is impossible to determine because of incomplete tumor sampling. In addition, the tumor cells may not always be clearly recognized as either oligodendroglial or astrocytic, i.e. they may have features of both lineages.

Anaplastic oligoastrocytomas feature increased cellularity, nuclear atypia, pleomorphism, and high mitotic activity. Microvascular proliferation and necrosis may be present. The differential diagnosis of anaplastic oligoastrocytoma versus glioblastoma is problematic, particularly since oligodendroglioma-like areas may be present in some otherwise typical glioblastomas. The appropriate terminology for such cases is disputed; “glioblastoma with oligodendroglioma component” has been suggested as a compromise term that may be used for such cases. Although the prognostic importance of an oligodendroglial component in an otherwise typical glioblastoma has not been proven so far, such tumors may be associated with prolonged survival when compared with ordinary glioblastomas (25, 26).

Ependymomas

The classification of ependymal tumors has not been changed except for the addition of a new spindle cell variant, the *tanycytic ependymoma*. The term refers to the similarity of the neoplastic cells to “ependymoglia” or “tanycytes,” i.e. stretched cells that have a limited distribution in the normal mature nervous system (27). The few documented cases show no preference for age, sex, or location within the CNS (27–31). Spindle cells are the key histopathological feature, often in conjunction with conventional ependymoma patterns. Calcifications and vague perivascular pseudorosettes may be seen, but true rosettes are absent. GFAP immunoreactivity is present and often strongest in cell processes. In 1 reported case of ganglioglioma, a tanycytic ependymoma comprised the glial component (32). Despite occasional nuclear atypia, tanycytic ependymomas are WHO grade II lesions. Gross total resection is the treatment of choice.

Neuroepithelial Tumors of Uncertain Origin

In the 1993 WHO classification (33), this category included 3 neoplasms: polar spongioblastoma, astroblastoma, and gliomatosis cerebri. The 1999 WHO working group recommended deleting “polar spongioblastoma” from the 2000 WHO classification, since it is not a well-defined entity and the palisading pattern typical for this lesion is observed in several other brain tumors, notably oligodendrogliomas. The chordoid glioma of the 3rd ventricle, a recently identified neoplasm, was, however, added to this category.

Chordoid Glioma of the 3rd Ventricle: This rare, morphologically distinctive and clinically benign tumor was only recently described (34) and added to the group of neuroepithelial tumors of uncertain origin. To date, all have occurred in adults and have been restricted to the 3rd ventricle wherein they form a largely solid, contrast-enhancing mass. Parenchymal involvement is limited. Females are most often (3:1) affected. Aside from occasional visual or endocrine disturbance, symptoms are nonspecific. Histologically, chordoid gliomas consist of clusters, cords, and streams of eosinophilic, rather epithelioid cells in a mucinous stroma often containing a lymphoplasmacytic infiltrate replete with Russell bodies. Fibrillary tumor cell processes are occasionally seen. Nuclei are regular, often vesicular, and feature a small nucleolus. Most tumors lack mitotic activity. Immunoreactivity for GFAP is widespread, while S100 immunoreactivity is variable. Focal EMA reactivity may also be seen. MIB-1 labeling indices are low (35). The principal differential diagnosis of chordoid glioma is chordoid meningioma, a more uniformly EMA-positive lesion lacking GFAP staining (36). The location of chordoid gliomas, together with attachment to the third ventricular wall and hypothalamus, often precludes their total removal. Slow recurrence of subtotally resected tumors has been seen, as have deaths due to local tumor regrowth.

Glioneuronal Tumors

The nomenclature of infantile desmoplastic cerebral lesions was simplified to denote a single lesion with an either astrocytic or dual glioneuronal differentiation. Thus, the designations of desmoplastic cerebral astrocytoma of infancy (3, 37) and desmoplastic infantile ganglioglioma (38) were combined to “desmoplastic infantile astrocytoma and ganglioglioma” (1), the rationale being that with the exception of the presence or absence of neuronal differentiation, these 2 lesions share similar age distribution, clinical features, MR imaging, location, morphology, and a usually favorable prognosis.

Cerebellar Liponeurocytoma: This uncommon neoplasm was first described in 1978 (39) and has been reported under different names, most frequently as lipomatous medulloblastoma (40–42). It appears to occur exclusively in the cerebellum of adults (mean age, 50 yr), without gender preference. Histopathologically, it is characterized by clusters of lipidized cells that resemble adipocytes in a generally monotonous background of small neoplastic cells that often show morphological features of neurocytes. There is consistent, diffuse expression of synaptophysin and MAP-2. GFAP immunoreactivity is often focally present. The lipidized cells also show synaptophysin staining of the plasma membrane, indicating that they represent neoplastic neurocytes with lipidization rather than being an admixture of adipocytes. The consensus term “cerebellar liponeurocytoma” was chosen,

given the preferred location and the lipidized neurocytic nature of the cells. Although it was recognized that glial differentiation is common, it is not the dominant direction of differentiation. Thus, the consensus term did not include reference to the glial features. Mitotic activity is usually absent and the growth fraction, as reflected by the MIB-1 index, is in the range of 1%–3%. Accordingly, the prognosis is favorable. In order to avoid aggressive adjuvant therapy, the Working Group moved this entity out of the category of primitive neuroectodermal tumors and included it among glioneuronal tumors (1).

PNET/Medulloblastoma

The primitive neuroectodermal tumor (PNET) concept (43, 44) has been controversial for more than a decade, largely due to the uncertainties regarding the histogenesis of the medulloblastoma and its relationship to histologically similar neoplasms at other sites. It is based on the assumption that PNETs share common progenitor cells in the subependymal matrix layers and that their neoplastic transformation at various levels of the CNS leads to tumors with similar morphology and biology. However, there is now increasing evidence that at least a subset of medulloblastomas originates from the external granular cell layer (EGL) of the cerebellum. This hypothesis is strongly supported by the occasional presence of PTCH mutations (45) since the sonic hedgehog/PTCH pathway controls cell proliferation in the EGL during embryonal development (46). Strongly suggestive is the development of medulloblastomas on the cerebellar surface of p53-null mutant (knockout) mice with somatic inactivation of the retinoblastoma gene (Rb) in the external granular layer (47).

Other alterations typically involved in the evolution of medulloblastomas, e.g. beta-catenin and APC mutations (48) and the pattern of DNA methylation (49), appear to be absent in pineoblastomas and extracerebellar PNETs. The response to radio- and chemotherapy also appears to differ in that patients with supratentorial PNETs (SPNETs), particularly pineoblastomas, have a less favorable prognosis (50, 51). These clinical and experimental findings argue against classifying medulloblastomas together with other PNETs. Thus, the new WHO classification (1) keeps the cerebellar medulloblastoma and its variants separate from SPNETs.

The Working Group also debated the criteria and terminology of “desmoplastic medulloblastoma,” particularly whether the essential feature separating this variant from classical medulloblastoma is desmoplasia or its marked tendency for neuronal differentiation within so-called pale islands. The Group clearly preferred placing emphasis on the latter feature of marked neuronal differentiation, since such tumors more often follow a less aggressive course than standard medulloblastomas. Nonetheless, the term desmoplastic medulloblastoma was retained.

Large Cell Medulloblastoma: This recently characterized, highly malignant variant represents about 4% of medulloblastomas (52). Although reported cases are few, the age at manifestation ranged from 13 months to 4 yr and all the patients were male. These neoplasms are usually located in the cerebellar vermis and are characterized by highly aggressive behavior, with early cerebrospinal fluid dissemination despite radio- and chemotherapy. Microscopically, the tumour cells feature large, round, and/or pleomorphic nuclei with prominent nucleoli. Large areas of necrosis, high mitotic activity and high apoptotic rate are common findings. Although Homer Wright rosettes are not observed, immunoreactivity for synaptophysin and NSE has been detected, while staining for GFAP and EMA is absent. MYCN and MYCC amplification are occasionally present, as are double-minutes and isochromosome 17q (52, 53). Morphologically, this variant somewhat resembles the atypical teratoid/rhabdoid tumors of the cerebellar region, but differs on the basis its immunophenotype and cytogenetic features.

Atypical Teratoid/Rhabdoid Tumors

Since the 1993 WHO classification, the atypical teratoid/rhabdoid tumor (AT/RT) has been recognized as a unique embryonal tumor of the central nervous system (CNS) (54). Previously, these tumors were most frequently diagnosed as medulloblastoma (MB) or PNETs, since approximately two thirds have components that closely resemble medulloblastoma or extracerebellar PNETs. In addition to rhabdoid cells, AT/RTs often also contain malignant epithelial and/or mesenchymal components that further distinguish them from other embryonal neoplasms.

This tumor occurs predominantly in infants and children, some of whom may also have a primary renal rhabdoid tumor, but the majority of CNS AT/RTs are not associated with a renal neoplasm. More than 90% occur in children under 5 yr of age; the majority manifesting in infants less than 2 yr of age. There is a slight male preponderance. About 50% of AT/RTs arise in the posterior fossa, with a predilection for the cerebello-pontine angle. Clinical, neuroimaging and gross pathological features are similar to PNET-MB, and approximately one third of tumors have cerebrospinal fluid spread at presentation. The prognosis is grim; the majority of patients die in the first year after diagnosis, in contrast to children with medulloblastoma who currently have a 5-yr survival rate of 60%–80%.

Some tumors are composed entirely of rhabdoid cells while others show of a combination of rhabdoid cells and areas resembling PNET/medulloblastoma. Approximately one third of tumors contain malignant mesenchymal elements, most often spindle cells, and a quarter exhibit a mature epithelial population that may be glandular or squamous. Any or all cell types or patterns may be seen

in a given tumor in combination with the rhabdoid component. Necrosis and abundant mitotic activity are common. Immunohistochemical features are complex and vary depending upon the cellular composition of the tumor. In general, rhabdoid cells express vimentin and EMA, and slightly less often smooth muscle actin. A surprising number show neurofilament, GFAP, and keratin, but not germ cell markers or desmin. The primitive neuroectodermal cells may express neurofilament protein, GFAP, or desmin, but some are immunohistochemically undifferentiated. The epithelial component expresses keratin but sometimes EMA and vimentin as well. Mesenchymal cells express vimentin, sometimes smooth muscle actin (SMA), but rarely desmin. These are rapidly growing tumors that have MIB-1 labeling indices of 50%–80%.

Although the histogenesis remains obscure, a unique genetic alteration has been documented in 90% of the tumors. Those arising in the CNS (and in the kidney) demonstrate monosomy or a deletion of chromosome 22 by fluorescence in situ hybridization (FISH) or in LOH studies. The gene involved, *hSNF5/INI1*, maps to chromosome band 22q11.2 and is consistently mutated in AT/RTs (55). Somatic *INI1* mutations have only rarely been reported in other CNS tumors, making mutation analysis a valuable diagnostic adjunct in difficult cases (56).

Meningiomas

The classification and grading of meningiomas received considerable attention from the WHO committee. Since recent reports had drawn attention to new, clinically relevant meningioma variants and had proposed more objective means for grading meningiomas, changes to the WHO classification were considered necessary. Given that the primary goal of evaluating meningiomas histopathologically is to provide information on the likelihood of recurrence and aggressive behavior, the Working Group tailored the classification and grading scheme to address this issue. Four histopathological variables were discussed and received recommendations: grade, histological subtype, proliferation index, and brain invasion.

Some histological subtypes of meningioma are associated with greater likelihood of recurrence and/or aggressive behavior (Table 3). It was recommended that clear cell and chordoid meningiomas be assigned a WHO grade of II, since both have high recurrence rates, particularly after subtotal resections. Rhabdoid meningiomas were assigned a WHO grade of III since these have been reported, in most cases, to have histological features of malignancy and to follow an aggressive course. However, it was pointed out that the expected behavior of rhabdoid meningiomas lacking other features of malignancy has not yet been established.

The 1993 WHO classification had ill-defined borders between benign and atypical meningioma and between atypical and malignant meningioma. To remedy this situation, the 2000 WHO classification recommends more objective criteria, which were based largely on a series of recent studies from Mayo Clinic (57, 58). The WHO Working Group recognized that these new criteria were based on studies from a single institution and that other semi-quantitative schemes exist (59, 60). Nonetheless, the new criteria are simple and robust and will provide an objective system for future investigations to refine (Table 3).

Proliferation indices, such as MIB-1 labeling, are useful in estimating the probability of meningioma recurrence. However, given interinstitutional and interobserver variation inherent in such assays, cut-off levels distinguishing benign from atypical meningiomas and atypical from malignant meningiomas were not advised. For this reason, MIB-1 labeling cannot be used to establish meningioma grade. However, high proliferation indices do provide independent prognostic information. It was therefore recommended that a phrase such as “with high proliferative activity” be added to diagnoses of benign or atypical meningiomas if the labeling indices were conspicuously higher than expected for those entities.

Brain invasion has long been considered a worrisome feature in meningioma resection specimens, but it has been debated whether brain invasion constitutes a de facto criterion of malignancy. It was also felt by the committee that brain invasion is a feature more germane to staging than to establishing an inherent malignancy grade. More significantly, recent molecular genetic investigations have failed to show genetic changes characteristic of high-grade meningiomas in histologically benign meningiomas that display brain invasion (61–63). It has also been shown that the presence of brain invasion in benign meningiomas increases the likelihood of recurrence to a percentage similar to that of atypical meningioma, not malignant meningioma (57, 58). Furthermore, the presence of brain invasion in an atypical meningioma also does not correlate with a malignant course. The Working Group recommended that a phrase such as “with brain invasion” be added to diagnoses of benign or atypical meningiomas if brain invasion was present; this will alert the clinician to a greater likelihood of recurrence, particularly in the setting of a histologically benign meningioma.

Perineurioma

This subset of nerve sheath tumors has been added to the classification of tumors of the peripheral nervous system. It consists of an intraneural variant typified by pseudo-onion bulb formation and an extraneural soft tissue tumor; neither is NF-1-associated. Despite marked differences in their clinical and gross characteristics, both

tumors share immunohistochemical and ultrastructural features of perineurial cells.

Intraneural Perineurioma: This usually solitary lesion, only recently recognized as neoplastic (64), was once considered a reactive lesion. Tumors usually present as solitary lesions in adolescence or early adulthood, with no sex predilection. Peripheral nerves, particularly of the extremities are most often affected; cranial nerve involvement is rare (65). At surgery the affected nerve is cylindrically enlarged, usually over a span of 2 to 10 cm, but no plexiform lesions have been reported. Histologically, the key feature is pseudo-onion bulb formation consisting of 1 to 5 or more layers of benign-appearing perineurial cells encircling one or more nerve fibers. Affected fascicles have hypercellular endoneurial compartments. Mitotic activity is rare and MIB-1 labeling indices are low. Immunohistochemical studies show whorled EMA-positive perineurial cells as well as S-100 protein-reactive Schwann cells and neurofilament-positive axons at the centers of the pseudo-onion bulbs. Chromosome 22 loss is a characteristic feature (64). The treatment of intraneural perineurioma is conservative sampling of an affected fascicle rather than resection of the lesion.

Soft Tissue Perineurioma: This rare lesion consists entirely of perineurial cells and was first described on the basis of its ultrastructure (66). Unlike more common nerve sheath tumors, it is only rarely associated with an identifiable nerve (67). Almost all are benign; malignant perineuriomas are rare and poorly characterized. Perineuriomas typically occur in women (F/M ratio, 4:1), usually in subcutaneous tissue of the extremities or trunk. Hands are also affected, particularly in males; viscera are rarely involved (68, 69). Perineuriomas are discrete but not encapsulated and range from 1.5 to 20 cm in diameter. The histologic features vary from elongated bundles to interwoven fascicles, whorls, and storiform arrangements. Interstitial “cracking” is an artifact commonly seen. Tumor cells often dissect among and encircle collagen bundles. Interstitial collagen deposition varies but is a conspicuous feature of tumors in the hands (70). Nuclei are elongate, curved, wrinkled, or flattened. Mitoses and necrosis are generally absent and blood vessels are inconspicuous. In addition to EMA and collagen 4/laminin staining, limited CD 34 reactivity is occasionally seen. Treatment consists of gross total excision and is curative.

Prognostic Factors and Response to Therapy

In the narrative section, the new classification contains summaries of clinical, histopathologic, and genetic factors that influence response to therapy, likelihood of recurrence and, ultimately, patient survival. However, many of the reported correlations are based on studies with small sample sizes and often without confirmation in independent larger studies. Survival has been measured as either recurrence-free survival or overall survival until

death. While these measures are often easily obtainable and are typically objective, other biological, clinical and neuroimaging endpoints are clearly needed to improve future classification schemes (16). For example, assessing whether a tumor with a particular molecular feature responds to a specific therapy may provide important information about choosing among currently available treatments and for the design of future therapies, regardless of whether any prognostic information is provided. However difficult, attempts must be made to distinguish between markers that reflect the natural history of the disease and those that predict response to particular therapies. Furthermore, quality of life issues must be considered in future molecular marker studies since, particularly in the brain, survival-prolonging therapies may be associated with marked toxicity and reduced quality of life. Responses to therapy and susceptibility to toxicity may be related not only to tumor-specific alterations but also to constitutional genomic differences between individuals. Thus, with insights into the molecular basis of therapeutic response in individual patients, it may be necessary to subclassify tumors not only on the basis of tumor-specific alterations but on the basis of individual-specific allelotypes as well. The emerging complexity of the tumor-therapy-host axis will certainly provide classification challenges in the years to come.

Outlook

Disease classifications are a necessary tool in the practice of medicine but should be neither static nor an impediment to progress. In particular, there exists no definitive tumor classification. Several newly emerging brain tumor entities were not included in the current edition, usually due to the availability of only 1 report from a single institution. Several of these might be accepted in the next edition, including papillary glioneuronal tumor (71), rosetted glioneuronal tumor (72), lipastrocytoma (73) and, as new variants, lipomatous meningioma (74) and medulloblastoma with extensive nodularity (75). Additional entities may emerge from genetic typing aided by microdissection and tissue microarrays. Further, cDNA microarrays may aid in establishing gene expression patterns capable of predicting individual responses to radio- and chemotherapy.

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