

Development of the WHO Classification of Tumors of the Central Nervous System

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Introduction

The last four decades have seen the formulation of four editions of the World Health Organization (WHO) Classification of Tumors of the Central Nervous System (6, 8, 9, 11, 15), three over the past 17 years alone (6, 8, 9, 11). Each brought with it revisions reflecting changes of concept, some fundamental, as well as minor or subtle alterations. Not all changes met with the unanimous approval of committee participants. Nonetheless, each edition represented an improvement over prior efforts. The history of this process and a chronology of changes from one edition to the other is the substance of this work.

History

Early attempts to establish a systematic approach to brain tumor nomenclature such as the *Unio Internationalis Contra Cancrum* (UICC) (2), *Atlas of the Histology of Brain Tumors* (13), and the *Atlas of Gross Neurosurgical Pathology* (14) were unsuccessful. Even the groundbreaking AFIP Fascicle—*Tumors of the Central Nervous System* by Kernohan and Sayre (5), apparently met with little recognition in Europe. In 1952, a subcommittee of World Health Organization Expert Committee on Health Statistics published its conclusions regarding general principles underlying a statistically useful classification of

human tumors occurring at various organ sites (1). To assure ease and flexibility of coding, three elements of a classification were deemed necessary, including consideration of anatomic site, histologic tumor type, and degree or “grade” of malignancy. It is of note that these efforts were antedated and strongly influenced by the Armed Forces Institute of Pathology (AFIP), Washington, D. C. Fully 27 years prior to the appearance of the first WHO “Blue Book,” *Histological Typing of Tumors of the Central Nervous System* (5), this body had undertaken the publication of the first series of AFIP Fascicles under the auspices of the National Research Council-National Academy of Science, Subcommittee of Oncology. These atlases, accompanied by criteria and informative text, were the inspiration of, among others, Drs. Lauren V. Ackerman and Arthur Purdy Stout. Furthermore, Dr. Ackerman was involved with an *Illustrated Tumor Nomenclature* in English, French, German, Latin, Russian, and Spanish published by the International Union Against Cancer (UICC) (2).

In 1956, the World Health Organization executive board passed a resolution requesting the Director-General to consider establishing centers worldwide charged with the development of histologic definitions and facilitating the adoption of a uniform nomenclature for tumors of various organ types. In 1957, the Tenth World Health Assembly endorsed the plan. That same year, a Study Group on Histological Classification of Cancer Types met in Oslo, Norway, to advise the World Health Organization. The plan was to assemble experts, up to ten pathologists for each center, to develop a publication replete with numerous photomicrographs of the selected tumors. In addition, the centers were charged

with the production of up to 100 microscopic slide sets illustrating these entities. Since 1958, 23 centers manned by approximately 300 pathologists from 50 countries had been established.

With respect to tumors of the central nervous system, the position of head of the WHO Collaborating Centre for the Histologic Classification of Tumors of the Central Nervous System was given to Dr. Klaus J. Zülch of the Max-Planck Institute for Brain Research in Cologne, Federal Republic of Germany (16). Among the initial ten participants and the subsequently organized group of reviewers were Dr. Kenneth M. Earle of the Armed Forces Institute of Pathology, Washington, D.C., Dr. Lucien J. Rubinstein, Department of Pathology (Neuropathology), Stanford University, Stanford, CA, and Dr. John J. Kepes, University of Kansas, Kansas City, KS. Dr. Leslie H. Sobin of the WHO, Geneva, Switzerland was the series editor. From 1974 through 1976, some 230 cases were reviewed. The sessions can best be described as “stormy,” and the results were said to have left key participants “reasonably unhappy.” One glaring example of the contentious issues that surfaced centered upon the poorly understood “monstrocellular sarcoma,” a lesion championed by Dr. K. J. Zülch of Germany, which was, rightly, considered a giant cell glioblastoma by Dr. Lucien J. Rubinstein of the United States. The unhappy compromise double inclusion of the lesions in both section V Tumors of Blood Vessel Origin and under in glioblastoma in section I, subsection F—Poorly Differentiated and Embryonal Tumors. Despite its painful gestation, a classification replete with precise definitions and nomenclature was developed. The product was the first

international “Blue Book,” the 21st in the series of WHO publications. It was not intended as a textbook, but as a concise, illustrated, nosologic standard. An overview of the work in addition to some commentary regarding variations in concept among working group members is summarized in a 1980 article by K. J. Zulch, head of the WHO Collaborating Centre and author of the book (16). Overview commentaries occasionally followed the publication of subsequent “Blue Books” as well (7, 10).

Formulation of the classification had its inherent problems. At times, definitions proved elusive. For instance, both clinical and histologic malignancy had to be taken into consideration. Clinical malignancy was ascribed to any uncontrollably growing intracranial mass capable of lethality. This loose definition, of course, included tumors histologically benign. Alternatively, lethal tumors could produce localized pressure upon vital centers, cerebrospinal fluid obstruction with secondary hydrocephalus and brain herniation, and infiltrative tumor growth with or without metastasis. These mechanisms of death did not necessarily equate with malignancy in the histopathologic sense. As a result, both biologic and histologic grading schemes were developed. A similar biologic scheme of Dr. Zulch’s grouped tumors of similar prognosis regardless of histology or cytologic considerations (12) (see table below).

Proposed Five-Grade Scale of Malignancy of Intracranial Tumors According to Intrinsic Growth Properties

0. Neurinomas, meningiomas, craniopharyngiomas, hypophyseal adenomas, epidermoids, dermoids, teratomas, and lipomas
- I. Spongioblastomas, ependymomas of the ventricle, angioblastomas, plexus papillomas, and temporobasal gangliocytomas
- II. Oligodendrogliomas, astrocytomas, other gangliocytomas, and ependymomas of the cerebral hemispheres
- III. Pinealomas, malignant oligodendrogliomas, malignant astrocytomas, malignant gangliocytomas and malignant meningiomas
- IV. Medulloblastomas (including retinoblastomas), glioblastomas, and primary sarcomas

This dual biologic malignancy/histologic malignancy approach continued to influence grading in subsequent editions of the WHO Classification of Tumors of the Central Nervous System. A three- or four-tier (WHO I-IV) scheme of histologic malignancy was also developed, particularly for application to the spectrum of astrocytic, oligodendroglial, ependymal, and meningothelial tumors in which morphologic criteria of malignancy became increasingly clear. Prognosis and survival data were thus played off against histology and its time-honored parameters (cellularity, atypia, mitoses, atypical mitoses, stromal/vascular proliferation and necrosis). Tumor staging (TNM) was the function of the UICC, though it was of limited value in CNS pathology. Tumor coding, initially developed by the Manual of Tumor Nomenclature and Coding, American Cancer Society (3), subsequently became the International Classification of Diseases for Oncology (ICD-O) published by the World Health Organization (4).

Alterations Over Time

Listed below according to tumor group is a summary of changes in the 1979, 1993, 2000, and 2007 editions.

Astrocytic Tumors

1979—

- Category includes astrocytoma and anaplastic astrocytoma (but not glioblastoma), astroblastoma, pilocytic astrocytoma, and subependymal giant cell astrocytoma.
- Note—glioblastoma is defined as “An anaplastic, highly cellular tumor consisting of fusiform cells, small, poorly differentiated round cells, or pleomorphic cells alone or in varying combinations. Necrosis, pseudopalisading, fistulous vessels, and vascular endothelial proliferation, hemorrhage, and invasive growth and usually prominent features ...”
“Some typical glioblastomas show no evidence of a more differentiated tumor, whereas others are predominantly glioblastomas with focal areas of recognizable astrocytoma, less commonly oligodendroglioma, or exceptionally, ependymoma. Any of these gliomas may, in fact, terminate as a glioblastoma.”
- Giant cell glioblastoma was considered both a glioblastoma variant and a Tumor of Blood Vessel Origin (“monstrocellular sarcoma”).

1993—

- Pleomorphic xanthoastrocytoma added to astrocytic tumors.
- Glioblastoma added to the spectrum of astrocytic tumors.

- Astroblastoma moved to Tumors of Uncertain Histogenesis.
- St. Anne Mayo Grading Scheme adopted as WHO method of astrocytoma grading.

2000—

- No substantial changes.

2007—

- Pilomyxoid astrocytoma added as a subset of pilocytic astrocytoma.

Oligoastrocytomas and Mixed Gliomas

1979—

- Variants include oligodendroglioma and mixed oligo-astrocytoma, as well as anaplastic oligodendroglioma.
- No anaplastic form of oligoastrocytoma recognized.

1993—

- Anaplastic oligoastrocytoma recognized.

2000—

- No substantial change.

2007—

- Very high-grade oligo-astrocytic tumors with necrosis are considered “glioblastoma with oligodendroglial component.”

Ependymomas

1979—

- Variants include myxopapillary and papillary ependymoma as well as subependymoma.

1993—

- Clear cell variant added.

2000—

- Tanycytic variant added.

2007—

- No substantial change.

Pineal Tumors

1979—

- Variants include pineocytoma and pineoblastoma.

1993—

- Mixed/transitional pineal tumors added.

2000—

- Mixed/transitional category deleted.
- Pineal parenchymal tumor of intermediate differentiation added.

2007—

- Consideration given to splitting pineal parenchymal tumor of intermediate differentiation into low (grade II) and high (grade III) forms.
- Papillary tumor of the pineal region added.

Choroid Plexus Tumor

1979—

- Variants include choroid plexus papilloma and anaplastic choroid plexus papilloma.

1993—

- No substantial change.

2000—

- No substantial change.

2007—

- Atypical choroid plexus papilloma added.

Neuroepithelial Tumors of Uncertain Origin (Glial Tumors of Uncertain

Origin)

1993—

- Polar spongioblastoma and gliomatosis cerebri moved to this category from Poorly Differentiated and Embryonal Tumors category.
- Astroblastoma moved to this category from Astrocytic Tumors.

2000—

- Chordoid glioma added.
- Polar spongioblastoma deleted.

2007—

- Angiocentric glioma added.

Neuronal (Mixed Neuronal-Glial) Tumors

1979—

- Variants include gangliocytoma, and ganglioglioma, anaplastic gangliocytoma and ganglioglioma, neuroblastoma and ganglioneuroblastoma.

1993—

- Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos disease) added.
- Desmoplastic infantile ganglioglioma added.
- Dysembryoplastic neuroepithelial tumor (DNT) added.
- Central neurocytoma added.
- Paraganglioma of filum terminale added.
- Olfactory neuroblastoma added.
- Neuroblastoma and ganglioneuroblastoma deleted.

2000—

- Cerebellar liponeurocytoma added.
- Olfactory neuroblastoma and neuroblastoma of adrenal/sympathetic nervous system moved to new category of Neuroblastic Tumors.

2007—

- Extraventricular neurocytoma added.
- Papillary glioneuronal tumor added.
- Rosette-forming glioneuronal tumor added.

Poorly Differentiated and Embryonal Tumors (Embryonal Tumors)

1979—

- Category includes glioblastoma, gliosarcoma, giant cell glioblastoma (“monstrocellular sarcoma” considered synonymous with the latter) and gliomatosis. Category also includes medulloblastoma with desmoplastic and medullomyoblastic variant, medulloepithelioma, and primitive polar spongioblastoma.

1993—

- CNS neuroblastoma and ganglioneuroblastoma added.
- Note—Olfactory neuroblastoma and neuroblastic tumors of the adrenal gland and sympathetic nervous system entered into the classification under a new category of Peripheral Neuroblastic Tumors.
- Ependymoblastoma added.
- Primitive neuroectodermal tumor (PNET) added as a category for medulloblastoma-like tumors outside the cerebellum.
- Melanotic medulloblastoma added as a medulloblastoma variant.

2000—

- Desmoplastic and large cell medulloblastoma variants added.
- Atypical teratoid rhabdoid tumor added.

2007—

- Extensively nodular and anaplastic variants added to medulloblastoma.
- PNET now includes not only small cell-containing tumors but also medulloepithelioma.

Meningiomas

1979—

- Category includes meningotheliomatous, fibrous, transitional, psammomatous, angiomatous, hemangioblastic, hemangiopericytic, papillary and anaplastic meningioma.

1993—

- Microcystic, secretory, clear-cell, chordoid, lymphoplasmacytic, and metaplastic meningioma added.
- Atypical meningioma introduced as a category but not clearly defined.
- Hemangioblastic category deleted.
- Hemangiopericytoma moved to Mesenchymal, Non-Meningothelial Tumors category.

2000—

- Rhabdoid meningioma added.
- Atypical and anaplastic meningioma categories clearly defined by histologic criteria.

2007—

- No substantial change.

Tumors of Nerve Sheath Cells (Tumors of Cranial and Spinal Nerves)

1979—

- Category included schwannoma, anaplastic schwannoma, neurofibroma, and anaplastic neurofibroma.

1993—

- Cellular schwannoma and malignant peripheral nerve sheath tumor with divergent differentiation added.
- Melanotic malignant peripheral nerve sheath tumor added.
- Cellular plexiform and melanotic schwannoma added.

2000—

- Intraneural and soft tissue perineurioma added.
- Malignant melanotic schwannoma and its psammomatous variant added.

2007—

- No substantial change.

Primary Melanocytic Tumors

1979—

- Category included melanoma and meningeal melanomatosis.

1993—

- Diffuse melanosis and melanocytoma added.
added.

2000—

- No substantial change.

2007—

- No substantial change.

Tumors of the Anterior Pituitary (Tumors of the Sellar Region)

1979—

- Category included pituitary adenoma and pituitary adenocarcinoma.

1993—

- Adamantinomatous and papillary craniopharyngioma added.

2000—

- Granular cell tumor added.

2007—

- Pituicytoma and spindle cell oncocytoma added.

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