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MIROSŁAW J. MOSSAKOWSKI

HIGHWAYS AND STRAYWAYS IN CLASSIFICATION OF TUMORS OF THE CENTRAL NERVOUS SYSTEM

Department of Neuropathology, Medical Research Centre, Polish Academy of Sciences, Warszawa

A concise review of classifications of the central nervous system tumors is presented. Special attention has been paid to subsequent histological classification of CNS tumors prepared under auspices of the World Health Organization. The author points out a necessity of the modification of WHO classification from 1979, resulting from the accumulation of new clinical and pathological observations and data on one hand and from the progress of basic research concerning neoplasia in the nervous system on the other. The author stresses the clarifying and ordering values of the classification proposals and principles, treating critically some others. Separately, the histological malignancy grading systems are reviewed.

Key words: *CNS tumors, classification, malignancy grading systems*

Description of the central nervous system (CNS) tumors and first trials of their classification may be found in a number of publications as early as the first half of the 19th century. Among them particularly noteworthy are the papers of Dölliger (1770-1841), Schwann (1810-1882) and Müller (1801-1858) (for review see Zülch, 1956). A milestone in the knowledge about these tumors are no doubt the studies of R. Virchow (1821-1902). He, too, is the author of the first classification of brain tumors. After describing glia as a distinctive component of the cerebral tissue, he distinguished among CNS neoplasms, known under the collective name of sarcomas, a separate group, which he denoted as gliomas. On the basis of macro- and microscopic criteria he described hard and soft, cellular, medullary, fibrous, angiomatous and mucous gliomas, among which we may identify today several forms of known types of neuroepithelial tumors. He knew already ependymal gliomas and described tumors of acoustic nerves, as neoplasms of perineurial origin. He was the first to identify psammoma as a meningeal tumor (Zülch 1956). The second half of the bygone century and the first decades of the present one brought successive descriptions of tumors which according to today's criteria would be classified as neoplasms of neuroepithelial, meningeal and neurolemmal origin. Of course, the greatest interest was aroused by tumors from autochthonous CNS tissues.

Foundations for the first modern classification of the tumors derived from autochthonous cellular elements of the CNS were laid by the histological and embryological research on the development of the nervous system and the introduction of impregnation techniques with gold and silver salts of the particular components of the nerve and glial tissues, allowing their identification and distinction.

This classification was introduced by Bailey and Cushing in 1926. It actually was the first comprehensive classification of tumors of neuroepithelial origin based both on morphological criteria and general concept of histogenesis of the CNS. In this classification 14 groups of tumors were distinguished, deduced from known and hypothetically presumed cellular developmental forms derived from a primitive neural tube. The fundamental fragment of this classification consists in an assumption that tumors deriving from less differentiated cellular elements exhibit higher clinical malignancy. This assumption led to the introduction of immature variants for nearly all types of tumors linked with mature cellular components of the CNS such as ependymoblastoma for ependymoma, pineoblastoma for pinealoma or most controversial astroblastoma for astrocytoma, for which no counterpart can be found in the histogenesis of the nervous system. Neither has the hypothetical medulloblast been found which would be the tissue source for medulloblastoma. The nature and biological properties of unipolar spongioblastoma did not correspond to the

assumed developmental phase of the spongioblast. The tumor denoted as neuroepithelioma was found to occur in a limited localization as retinoblastoma.

The classification of Bailey and Cushing (1926) notwithstanding all the submitted reservations and modifications, is to this day the basis of most accepted and applied classifications of tumors originating from autochthonous cell components of the nerve tissue. The number of modifications introduced is too extensive for enumeration, although they had been suggested by such authorities as Penfield (1931), Roussy, Oberling (1932), Rio Hortega (1932), and others. Only as an example I would like to mention here the classification applied in the end of the fifties by D. Russel and L. Rubinstein (1959). Comparing with the original classification of Bailey and Cushing, it only brought an otherwise incompletely consistent arrangement of the particular types of tumors in groups corresponding to definite kinds of cerebral cells populations. Noteworthy is the exclusion of multiform glioblastoma from the astrocytic group. This will find its reflection in the still lately obligatory version of the WHO classification from 1979 (Zülch 1979).

A characteristic feature of all classifications deriving from Bailey and Cushing's scheme was the limitation to only one, though most common category of the CNS tumors, namely that of neuroepithelial origin.

A comprehensive classification concept of the CNS tumors understood as the neoplastic growth and as nonneoplastic space-occupying intracranial and intraspinal processes was presented by Zülch in 1956.

The basic concept of Zülch consisted in distinction of three main neoplastic groups of neuroectodermal, mesodermal and ectodermal origin, supplemented by metastatic tumors, and developmental malformations with a large series of vascular malformations as well as various space-occupying processes, including inflammatory, granulomatous and parasitic ones. This general wholistic approach of Zülch will later find its evident reflection in the first WHO classification (Zülch 1979).

As far as the original Zülch's classification is concerned, I would like to call attention to the distinction in the group of neuroectodermal tumors of a subgroup of immature tumors from the Bailey and Cushing's scheme, under the collective name of medulloblastoma. These correspond in the present categories to the group of embryonal tumors. An important element in Zülch's classification was the distinction of a separate group of paragliomas, which comprised all tumors of glial origin except astrocytoma and oligodendroglioma for which he reserved the name of gliomas. To the group of paragliomas he included Schwannoma, treated as a tumor of neuroepithelial origin, while in the classification of Russel and Rubinstein (1959) they were still considered as mesodermal neoplasms. The unipolar spongioblastoma of Bailey and Cushing was considered by Zülch as identical with fibrous astrocytoma of cerebellum, described by the Anglosaxon author as pilocytic astrocytoma. The leading feature of this tumor consists in high degree of histological differentiation and benign clinical course.

The development of neurosurgery and radiotherapy, characterizing the end of sixties, the appearance of new types of tumors of the central and peripheral nervous system and the broadening of ever tighter international scientific contacts called for universal, commonly accepted classification of tumors of nervous system, which would make possible an understanding between various milieus and scientific orientations, first of all physicians of various specialities involved in diagnostics and therapy of brain tumors. The WHO has undertaken this task calling up for this purpose an international panel of specialists and organizing a special Reference Centre, directed by Prof. K.J. Zülch. The panel worked for almost ten years and prepared a „Histological Typing of Tumors of the Central Nervous System" and published it in the multilingual „Blue Book" edited by K.J. Zülch (1979). This classification, the principles of which I will briefly recall, was well accepted in the wide milieu of specialists the world over and found application in most neuropathological laboratories.

A further profuse accumulation of new material and above all the introduction of new diagnostic and research methods, including immunocytochemistry, electron microscopy and recently molecular genetics allowed to elaborate a modified and modernized histological classification of the brain tumors. Its final version was prepared by P. Kleihues, P.C. Burger and B.W. Scheithauer and accepted by a team of consultants in Zürich in 1989. Its printed version appeared in „Brain Pathology" in 1993. For comparative reasons I will discuss both versions simultaneously, calling attention to the changes and modifications introduced recently.

A characteristic feature of both versions is a wholistic approach to the problem allowing to comprise all types of neoplasms occurring in the nervous system, independently of their origin. This classification in general and especially in its earlier version resembles Zülch's classification (1956), with exclusion of space–occupying inflammatory processes of various origin included by him, and inclusion of lymphoma category, absent in his original scheme. The new version from 1993 has reduced number of the main tumor groups from 12 in 1979 to 10. This reduction was done at cost of excluded

group of vascular malformations and liquidation of a separate group of neoplasms of vascular origin. As compared with the version of 1979, the tumors of meninges were elaborated in more detail and pituitary adenomas were included into a broader group of sellar region tumors. Much deeper changes were introduced within the particular groups of neoplasms, first of all in tumors of neuroepithelial origin, those of meninges and cranial and peripheral nerves.

The greatest modifications appeared in the class of neuroepithelial tumors. They consisted in the introduction of new types, formation of new subgroups and shifting of particular tumors between the groups. The multiform glioblastoma with its two variants was reintroduced to the group of astrocytomas. On the basis of immunocytochemical investigations and recent molecular genetic observations it is considered as a tumor of astrocytic series even in those cases when its morphology suggests significant participation of oligodendroglial component. A group of astrocytic tumors was additionally enriched by a new clinical-morphological entity, described in detail by Kepes et al. (1979) under the name of xanthoastrocytoma. This is a benign tumor of the astrocytic series, characterized by pronounced cellular pleomorphism, fatty degeneration of neoplastic cells, the presence of reticulin fibers and frequent appearance of perivascular inflammatory infiltrations. Astroblastoma was removed from the group of astrocytomas and included together with polar spongioblastoma and diffuse gliomatosis into a newly formed group of neuroepithelial tumors of uncertain origin.

The group of oligodendroglial tumors was reduced by the removal of mixed oligoastrocytoma, which in both its variants, the highly and poorly differentiated ones, was allotted to a separate group of mixed gliomas. Tumors of choroid plexus, were excluded from the group of ependymal tumors, whereas a new variant of ependymoma, described as clear cell ependymoma was introduced.

Important modifications occurred in the group of tumors originating from the nerve cells. This group was enriched by four types of tumors. One of these described originally as Lhermitte-Duclos tumor (Lhermitte, Duclos 1920), (desmoplastic gangliocytoma of cerebellum) was already well known at the time of the preparation of the first version of the WHO classification but was not included into it due to the controversy concerning its nature. The three remaining ones are the new entities described for the first time in the decade separating both classification versions. These tumors are: desmoplastic infantile ganglioglioma (Van der Berg et al. 1987), characterized by a profuse fibrous component with poor cellular population, exhibiting in immunocytochemical examination features of neuronal and glial differentiation, dysembrioplastic neuroepithelial tumor (Daumas-Duport et al. 1988) being distinguishable by cortical localization with prevalence of oligodendroglial population and a smaller contribution of astrocytes, which quite frequently is the substrate for partial epileptic seizures, resistant to pharmacological treatment. The third is central neurocytoma, characteristic for its ventricular localization, usually rich calcifications and predominance of cells with neuronal differentiation (Hassoun et al. 1982). A deep modification concerns the group of tumors which in classification of 1979 was denominated as poorly-differentiated tumors. In version of 1993 it was limited to embryonal tumors. As already mentioned, multiform glioblastoma left out this group. What really deserves special attention is the fact that within it a new category of tumors was distinguished under the name of primitive neuroectodermal tumors (PNET's), which collects classical medulloblastoma with its three variants and the neoplastic growth exhibiting a structural similarity if not identity with cerebellar medulloblastoma but localized beyond cerebellum.

Important modifications concern also the tumors of cranial and spinal nerves. New variants of neurolemmoma were introduced. These were described as cellular, plexiform and melanotic Schwannomas (Kleihues et al. 1993). All of them show, as compared with typical neurolemmoma, a higher degree of malignancy. In the group of peripheral nerve tumors the introduction of two new classes is noteworthy. This concerns malignant peripheral nerve sheath tumor (MPNST) with its epithelioid variant and MPNST with divergent mesenchymal and/or epithelial differentiation, including its melanotic variant. Similarly, the group of meningeal tumors was significantly extended and rearranged (Kleihues et al. 1993). A number of subgroups was distinguished, comprising tumors of both meningothelial and non-meningothelial cells with their benign and malignant categories as well as primary melanocytic lesions and tumors of uncertain histogenesis. The most common group of meningeal tumors originating from meningothelial cells was supplemented by a number of new variants such as microcystic, secretory, clear-cell, lymphoplasmocytic-rich meningiomas. Hemangioblastoma has been separated as a tumor of uncertain histogenesis.

In the remaining major groups of brain tumors the new version of WHO classification brings no essential changes. The modifications introduced seem to be rather ordering than substantial.

A comparative analysis of both versions of WHO classifications indicates that modifications introduced in 1993 contain, alongside with totally jus-

tified corrections and supplements, some controversial elements which may arouse some questions, and doubts. Beyond argument is the plausibility of introducing new types of tumors described recently and characterized clinically and verified pathomorphologically by modern diagnostic techniques. It seems to me deeply correct to include the multiform glioblastoma into the group of tumors of astrocytic series, especially as it found support in genetic information. The distinction of tumors of the PNET group seems to be well founded. It would seem that at the present level of knowledge it will close the discussion on the histogenesis of medulloblastoma-like tumors in extracerebellar localization. I strongly support the arrangement of primary melanotic lesions in meningeal localization. Some other changes seem to be less comprehensible or even doubtful. For instance, I do not clearly understand why such tumors as chondroma, osteoma or lipoma are included into the group of tumors of meninges. Hemangioblastoma, classified to the group of meningeal tumors of uncertain histogenesis occurs not only in meninges. Cerebellar hemangioblastoma seems to be a well defined tumor. I also do not understand why gliomatosis cerebri was classified to the neuroepithelial tumors of uncertain origin. It seems to me that the origin of this diffuse glial neoplastic growth is clear as far as its tissue origin is concerned. Its pathogenesis is unclear, but this is true for most of the tumors. An old latin saying *habent sua fata libelli* may be transcribed as *habent sua fata tumores*, if one follows the classification fate of two types of glial tumors, known as astroblastoma and polar spongioblastoma, classified finally together with gliomatosis cerebri to the subgroups of neuroepithelial tumors of uncertain origin. Lyphomas are very poorly represented in both versions of WHO classification as compared with other tumor groups. This is striking in view of their increasing incidence, especially in recipients of transplanted organs and in HIV-infected patients.

I would also like to devote a moment to the question of morphological grading of the malignancy of CNS tumors. After Bailey and Cushing (1926) most histological classifications of the brain tumors of neuroepithelial origin based on histogenetic principles attributed the biological properties of the tumor, expressed by its proliferation activity and clinical malignancy, to the level of its maternal cells in the development of the CNS tissues. This concept assumed that the tumors originating from cells, representing lower stages of cellular development and differentiation exhibited higher biological activity and dynamics of the pathological process. This assumption proved true in relation to tumors deriving from verified or only hypothetical cells with the lowest differentiation (correctly: undifferentiated cells). The same assumptions were not correct fully with regard to other neoplasm groups histogenetically referred to cellular tissue components of a high degree of differentiation. This concept did not take into account, namely, as pointed already in Bailey and Cushing's monograph, features of anaplasia different in their intensity, which occur in otherwise histogenetically homogeneous tumor groups such as astrocytoma, oligodendroglioma, ependymoma and others.

The first attempt at taking this factor into account was the system proposed by Kernohan et al. (1949) based, beside histological criteria determining the appurtenance of the tumor to a given series of neuroepithelial tumors, on quantitative evaluation of anaplasia occurring in neoplastic tissue and expressed by the proportion of dedifferentiated cells. This classification divided four from among five distinguished basic groups of tumors into four classes of malignancy (dedifferentiation). This classification contains numerous references to the original classification of Bailey and Cushing (1926), omitting the groups the existence of which the authors put in doubt and introducing new ones not mentioned in Bailey and Cushing monograph. The Kernohan's classification (Kernohan et al. 1949) based on grading of malignancy in dependence on the intensity of features of anaplasia found wide approval of both clinicians and pathologists. The latter called attention above all to the fact that this classification was close or similar to analogous ranking system of tumors of other organs and tissues. However, it also aroused reservations concerning its excessive simplification, not sufficiently univocal criteria of cell dedifferentiation and above all the limited application in evaluation of biopsy material, due to significant differences of the morphology of different areas of the same tumor. The second reservation was the lack of attention to the variability of histological picture of tumor in the course of its natural evolution and even more this resulting from therapeutic intervention. Nevertheless, this classification found broad application in diagnostic practice as important supplementation in improvement of precision of classifications based on histogenetic and histological principles. The element of Kernohan's (Kernohan et al. 1949) grading can be noticed in both versions of WHO classification.

The Kernohan's classification was followed by others, giving more precise criteria for grading tumor malignancy. For historical reasons I would like to mention three grade system of Ringertz (1950) concerning mostly tumors of astrocytic series. The St Anne/Mayo system for astrocytomas presented by Daumas et al. (1988) returns back to four-grade

classification, based on four precisely characterized groups of changes: nuclear atypia, presence of mitoses, proliferation of vascular endothelium and appearance of necrotic foci. It should be mentioned that nuclear atypia concerns both shape and size of nuclei as well as chromatin content and distribution, while endothelial proliferation is determined by multilayer arrangement of vascular endothelial cells. In this system grade first comprises tumors with none of the above quoted abnormalities. Tumors with one of them, in most instances nuclear atypia, belong to second group: two sets of abnormalities classify tumor to third grade. The 4th grade concerns tumors with coexistence of three or all parameters of evaluation. Experience with abundant clinical material proved the high usefulness of this system, which was largely applied in its modified form in WHO classification from 1993. Malignancy grading applied in this system is not limited to tumors of neuroepithelial origin, it also comprises those of neurolemmal and meningeal derivation. It should be stressed that when the criteria of evaluation are more precise and strict, the group of first grade tumors became greatly reduced. This concerns first of all neuroepithelial tumors of glial derivation, and to lesser degree those of neuronal origin.

I would like to mention additionally another classification of supratentorial glial tumors, in which malignancy grading has been based on morphological features of anaplasia supplemented by those of dysplasia, understood as exponents of degenerative changes involving both tumor cells and its vascular system. I have in mind histoclinical classification of Andrzej Głuszcz (1972), which has been applied for many years in the Łódź Centre in Poland.

This concised of necessity review of the main classification systems of the tumors of the CNS, including the recently introduced changes and modifications, plainly shows the difficulties met in attempts of enclosing the extremely complex biological processes with deeply disordered control mechanisms within classification frames, based on evaluation of static histological preparations. These difficulties are only reduced to a limited degree even when rigorous, strictly defined morphological criteria are enriched by the confrontation with the clinical evolution of the process both in pre-and postoperative period. Neither are the newest techniques of research methods used in contemporary pathomorphology and even molecular genetics sufficient. The existence of these difficulties and consciousness of limitations do not dispense us of the necessity of creating new classification systems comprising the whole wealth of informations necessary for rational therapeutic procedures. This is an indispensable key to understanding between the physician treating the patient, notwithstanding whether he is a neurosurgeon, radio- and chemotherapeutist on one hand and informing pathomorphologist on the other. The need of an universal classification, as already mentioned, results also from the necessity of using a common language by the neuropathologists from various centres and countries. Finally, it is the expression of an ever deeper and more precise understanding of the phenomenon of neoplasia in the nervous system. The foundation of a new classification system proceeds by the way of successive approximations. The need for new trials is the resultant of the accumulation of information material, ever increasing owing to the number of data and observations on the one hand and the development of basic sciences enriching the understanding of the process of neoplasia in general and in definite groups and types of tumors in particular. At the present stage of knowledge there are no objective possibilities to create an ideal classification system. The matter is additionally influenced by subjective factors such as individual convictions, opinions and even likes and believes of the specialists founding the given system. It is only important that each change in classification can be a true approximation and the best possible way to fulfill the needs of the users.

Drogi i bezdroża klasyfikacji guzów ośrodkowego układu nerwowego

Streszczenie

Autor przedstawia krótki przegląd klasyfikacji guzów ośrodkowego układu nerwowego, ze szczególnym zwróceniem uwagi na kolejne wersje histologicznej klasyfikacji opracowane pod auspicjami Światowej Organizacji Zdrowia. Autor podkreśla konieczność modyfikacji klasyfikacji ŚOZ z roku 1979, wynikającą z jednej strony z nagromadzenia nowych danych i informacji klinicznych i patomorfologicznych, z drugiej zaś z rozwoju badań podstawowych, dotyczących procesu nowotworzenia w ośrodkowym układzie nerwowym. Podkreślając wagę i porządkującą rolę propozycji zawartych w nowej klasyfikacji, odnosi się krytycznie do niektórych spośród nich. Odrębnie ustosunkowuje się do obowiązujących systemów histologicznej gradacji stopnia złośliwości nowotworów mózgu.

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Authors address: Prof. M.J. Mossakowski, Medical Research Centre, Polish Academy of Science, 3 Dworkowa St, 00-784 Warszawa, Poland