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Slobodan DOŽIĆ
Dubravka CVETKOVIĆ-DOŽIĆ
Milica SKENDER GAZIBARA
Branko DOŽIĆ

INSTITUTE OF PATHOLOGY, MEDICAL FACULTY, UNIVERSITY OF BELGRADE, YUGOSLAVIA

Review of the World Health Organization classification of tumors of the nervous system

KEYWORDS: Nervous System Neoplasms; Classification; World Health Organization

Classification of tumors of the nervous system is a dynamic issue requiring permanent critical review because application of increasing number of new immunohistochemical and molecular genetic techniques give more precise data on the origin and nature of these tumors.

The first World Health Organization (WHO) classification of nervous system tumors (Zulch, 1979) had served its purpose very well during a period of almost ten years (1). The official revision of the 1979 WHO classification was done at the meetings in Houston (Texas, 1988) and in Zurich (Switzerland, 1990) and was published as the second WHO classification (2) 3 years later (Kleihues, 1993). Deliberations by the WHO experts committee at these two meetings were focused on three aspects: 1) the concept of primitive neuroectodermal tumor (PNET) and its relationship to medulloblastoma, 2) grading of glial tumors and 3) histo-biologic aspects of meningioma. A great innovation in the second WHO classification was introduction of immunohistochemustry as an additional factor in classification of tumors of nervous system. Several new tumor entities (pleomorphic xantoastrocytoma, central neurocytoma, infantile desmoplastic astrocytoma/ganglioglioma, dysembryoplastic neuroepithelial tumor) were included in these classifications.

The third WHO classification of the nervous system tumors was published in 2000 (3). This classification is based on consensus recommendation of an international WHO Working group of experts that convened in Lyon in 1999. The editors are P. Kleihues and W.K. Cavanee. The working methods comprised three steps: a consensus manuscript for each chapter was initially written by a limited number of selected authors; a revision of the manuscript by a wider subgroup of experts followed; and lastly, the final version was submitted to the entire working group. The 2000 WHO classification, in addition to histological and immunohistochemical basis (criteria) is supplemented by genetic results. During the past decade our knowledge of the genetic basis of human neoplasms has increased greatly and histological and immunohistohemical classification of neoplasms is now increasingly supplemented by genetic profiling. It is considered as a great step forward that for many neoplasms the cytogenetic and molecular genetic basis often represents a definitive criterion for classification. This trend will continue and the classification and possibly the grading of human neoplasms will increasingly be based on genomic alterations and gene expression patterns in addition to histopathological criteria. Histopathology and conventional light microscopy are still used in daily routine diagnosis as "gold standard" for diagnosis and classification of brain tumors, but it is nowadays evidently that immunohistochemistry, molecular genetics and electron microscopy are very important, sometimes indispensable adjunct for precise diagnosis within the existing classification, especially when dealing with poorly differentiated neoplasms.

The 2000 WHO classification is published in the form of the new Blue Book, which contains, in addition to definitions and codes of the International Classification of Diseases-Oncology (ICD-O), the comprehensive chapters describing the epidemiological, clinical, radiological, histopathological, biological and predictive features of each entity.

NEW TUMOR ENTITIES

The new tumur entities include chordoid glioma of the third ventricle, cerebellar liponeurocytoma, atypical teratoid/rhabdoid tumor, and perineurioma (4).

Chordoid glioma of the third ventricle

This entity is added to the group neuroepithelial tumors of uncertain origin. It was first described as peculiar form of meningioma with expression of GFAP positivity. As chordoid glioma it was described in 1998 on the basis of eight cases restricted to the third ventricle. Histopathologically, this rare and slow growing tumor of adults corresponds to WHO grade II. It is composed of clusters of oval or polygonal cells with abundant eosinophilic cytoplasm, relatively uniform, often vesicular nuclei with small nucleolus and mucinous stroma. The mitoses are very rare or absent. A stromal lymphoplasmocytic infiltrate, often with Russell bodies is a consistent finding. Reactive astrocytes and Rosenthal fibers are seen in adjacent non neoplastic tissue. The tumor cells show strong diffuse reactivity for GFAP and vimentin, variable reactivity for S-100 protein, focally positive for epithelial membrane antigen (EMA), and negative for synaptophysin. There are histological similarities between chordoid glioma and chordoid meningioma, but chordoid meningioma is typically GFAP-negative, dura-based tumor (5).

Cerebellar liponeurocytoma

Cerebellar liponeurocytoma is a very rare, slowly growing neoplasm, with neuronal and lipomatous differentiation appearing exclusively in the cerebellum of adults. It was first reported in the 1978 under the name of lipomatous medulloblastoma. Patients show typical clinical picture of a posterior fossa tumor. In cases reported to date there was no significant gender predilection. On the basis of the clinical, histological and immunohistochemical data, subsequently under different names (neurolipocytoma, lipomatous medulloblastoma, lipomatous glioneurocytoma, lipidized glioneuroectodermal tumor) this tumor was recognized as a separate clinicopathological entity and added to the category of neuronal and mixed neuronal-glial tumors in the 2000 WHO classification. Histopathologically, cerebellar liponeurocytoma is composed of small neoplastic cells that resemble neurocytes having round or oval nuclei and clear cytoplasm resembling neoplastic oligodendrocytes. Inside of these relatively uniform histological figure there are many smaller or larger groups of lipidized cells, resembling adipocytes. A hallmark of histological figure is presence of advanced neuronal differentiation. Necrosis and microvascular proliferation are absent pathological mitoses are rare. Immunohistochemically there is a diffuse positive expression of NSE, synaptophysin and MAP-2. GFAP is focally expressed in the majority of cases. The lipidized cells also show synaptophysin expression of the plasma membrane, indicating the lipidized neurocytic nature of these cells rather than being an admixture of adipocytes. Cerebellar liponeurocytoma corresponds histologically to WHO grade I or WHO grade II (6).

Atipical teratoid/rhabdoid tumor (AT/RT)

AT/RT is a unique malignant embryonal CNS tumor occurring predominantly in infants and children. This tumor was first reported l985 and was originally designated as atypical teratoid tumor, but because of the histological

Address correspondence to:
Slobodan Dožić, Institute of Pathology, Medical Faculty, University of Belgrade, Dr Subotica 1, P.O.Box 168, 11000 Belgrade, Yugoslavia, E mail: dozic@eunet.yu

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similarities to the rhabdoid tumor of the kidney, the tumor designation was modified to AT/RT. In very rare cases AT/RT in infants was associated with primary renal rhabdoid tumor. About 200 cases have been reported until now, the great majority in children less than 5 years of age and only four cases in adults. There is a slight male preponderance. The tumor has tendency to be located in posterior fossa (cerebellum and cerebello-pontine angle), while supratentorial and spinal localization is less frequent. Cerebral and leptomeningeal dissemination is common, both at presentation and relapse. This tumor does not respond effectively to therapy and in great majority of cases it is fatal within one year. AT/RT corresponds histologically to WHO grade IV.

Grossly, AT/RT is similar to medulloblastoma or PNET. It is soft, pinkish, containing foci of necrosis and hemorrhage. In regions with mesenchymal tissue it tend to be firm and white-grayish. Microscopically, in addition to rhabdoid cells there are components of primitive neuroectodermal, mesenchymal and epithelial cells. Rarely the AT/RT is composed only of rhabdoid cells. The typical rhabdoid cells are round or oval, rich in cytoplasm, with typically eccentric nucleus and prominent nucleolus. Some cells contain poorly defined, pink inclusion body. Electronmicroscopically, rhabdoid cells are characterized by cytoplasmic accumulation of intermediate filaments which push the nucleus to the cell periphery. Mesenchymal and epithelial components may exhibit high grade of malignancy. Mitotic activity is usually common in all cell components. Immunohistochemistry is very complex, depending upon the different tissue components. Rhabdoid cells express EMA and vimentin, and may express SMA, neurofilament, GFAP and keratin. Mesenchymal tissue expresses vimentin, sometimes SMA and desmin. Epithelial component expresses cytokeratin, sometimes EMA and vimentin (7).

Perineurioma

Perineurioma is a rare soft tissue benign tumour which is added to the group of peripheral nervous system tumors in the 2000 WHO classification. This tumor should be distinguished from the other nerve sheaths tumors. It can be divided broadly into two categories: intraneural perineurioma, localized intraneurally and more common soft tissue (extraneural) perineurioma, unassociated with nerve. Intraneural perineuriomas occur along the peripheral nerves of extremities in adults. Cranial nerves are extremely rare affected. Grossly, it is usually presented as solitary cylindrically enlargement of affected nerve up to 10 cm long. Soft tissue (extraneural), perineuriomas occur in superficial or deep soft tissue of adults with a female predilection (2:1). A malignant variant of perineurioma is extremely rarely reported. Microscopically, intraneural perineuriomas are composed of perineurial cells encircling in more layers one or more axons forming pseudo-onion bulbs. Variable amount of collagenous stroma may be present between pseudo-onion bulbs and cell layers. Soft tissue perineuriomas are composed of plump or spindled cells with one or more nuclei. These cells are arranged in whorls, bundles, interweaving fascicles, or they may show a storiform pattern. A variably amount of stromal fibrotic tissue surrounds these components.

Immunohistochemically, the tumour cells show EMA positive staining of the cellular component and collagen type IV positive staining of fibrotic stromal matrix. The tumor cells are negative for S-100 protein and cytokeratin. In intraneural perineurioma characteristic immunohistochemical feature is EMA-positive tumor cells and S-100 positive preexisting Schwann cells and neurofilament positive axons at the centers of the pseudo-onion bulbs. Monosomy of chromosome 22 has been demonstrated in both intraneural and soft tissue perineuriomas. Surgical treatment is curative and no recurrences or metastasis have been reported. Histologically, perinueiomas correspond to WHO grade I (8, 9).

REVISION OF THE MENINGIOMAS CATEGORY

Essential revision was introduced in the meningiomas category, regarding grade, histological subtype, proliferation index and brain invasion. For both atypical meningioma WHO grade II and anaplastic meningioma WHO grade III histopathological criteria are more precisely defined (10). Clear cell meningioma and chordoid meningioma are now assigned as WHO grade II because of relatively high recurrence rate after resection and rhabdoid meningioma as WHO grade III because of atypical histological features and aggressive course in most cases. It was recommended that brain invasion should be considered as stage of tumor development rather than malignancy grade.

RENAMED TUMORS AND NOVEL TUMOR VARIANTS

Several tumors were renamed or established as novel tumor variants. The term mixed pineocytoma/pineoblastoma has been replaced by pineal parenchymal tumor of intermediate differentiation.

Tanycytic ependymoma (WHO grade II), large cell medulloblastoma (WHO grade IV), rhabdoid meningioma (WHO grade III) and teratoma with malignant transformation (no WHO grade) were established as novel tumor variants.

Peripheral neuroblastic tumors such as olfactory neuroblastoma (aesthesioneuroblastoma, WHO III), olfactory neuroepithelioma (WHO grade III) and neuroblastoma of the adrenal gland and sympathetic nervous system (WHO grade III) are now included in the 2000 WHO classification as a separate chapter.

Polar spongioblastoma has been deleted from the current WHO classification since it is considered a growth pattern rather than a clinicopathological entity.

Several brain tumors, such as papillary glio-neuronal tumor, lipoastrocytoma, lipomatous meningioma etc. that are recently reported in a few cases as possibly new clinicopathological entities or new variants, are not included in this classification because they still have not been sufficiently studied.

CONCLUSION

Classifications of the nervous system tumors should be neither static nor definitive. The most recent, third, current WHO classification of nervous system tumors was published in 2000. Many substantial changes were introduced. New entities include the chordoid glioma of the third ventricle, the atypical teratoid/rhabdoid tumor, cerebellar liponeurocytoma (the former lipomatous medulloblstoma of the cerebellum), solitary fibrous tumor and perineurioma. The new tumor variants include the large cell medulloblastoma, tanacytic ependymoma and rhabdoid meningioma. Several essential changes were introduced in the meningiomas regarding histological subtypes, grading and proliferation index. In addition to new entities described in the 2000 WHO classification there are newly brain tumor entities and tumor variants, which are not included in the current classification due to the insufficient number of reporeted cases, for example papillary glioneuronal tumor, rosetted glioneuronal tumor, lipoastrocytoma and lipomatous meningioma. They will be probably accepted in the next WHO classificaton. In the current WHO classification the importance of cytogenetic and molecular biologic investigation in the understanding and further classifications of these tumors has been emphasized.

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Tatjana PEKMEZOVIĆ[1,2]
Mirjana JAREBINSKI[1]
Milen PAVLOVIĆ[1]

[1]INSTITUTE OF EPIDEMIOLOGY, SCHOOL OF MEDICINE, BELGRADE, YUGOSLAVIA
[2]UNIT OF NEUROEPIDEMIOLOGY, INSTITUTE OF NEUROLOGY, CLINICAL CENTRE OF SERBIA, BELGRADE, YUGOSLAVIA

Epidemiology of central nervous system tumors

KEYWORDS: Nervous System Neoplasms; Classification; World Health Organization

Primary central nervous system (CNS) tumors are relatively infrequent in comparison with other malignant tumors. However, CNS tumors are the most frequent solid tumors in childhood and adolescence, accounting for approximately 20% of all malignant diseases in this age (1). There are many differences between childhood and adult CNS tumors according to frequency of some histologic types, biology, treatment, and prognosis.

Epidemiological analysis of the histologic features of CNS tumors in different ages showed that, in childhood, meduloblastoma ranks first among all tumors with participation of 24%, but it is not among the most common intracranial neoplasms in adults. Astrocytoma is second in children, whereas it is third in adults. Glioblastoma ranks third in children, but it makes up more than half of the CNS tumors in adults. Meningioma, which ranks second in adults, is relatively rare in children (2).

According to epidemiological literature, incidence of primary CNS tumors in a defined population varies from 4.9 to above 16/100 000 per year, while higher rates are generally found in societies with available and competent medical care, and with good organized cancer registries. Also, incidence rates are influenced by frequency of autopsy and improvement of case ascertainment with brain imaging technology such as CT and NMR (1,3). The American Cancer Society estimates that 16,800 new intracranial tumors were diagnosed in 1999, and the primary cancer of the CNS was the cause of death in 13 100 people in the same year (4). Some investigators report that the incidence of primary CNS tumors, especially in the elderly has substantially increased during the past two decades (3).

Despite variations among the different data sources in reporting and diagnostic practices, a general pattern of age-specific incidence was found: smaller peak in childhood can be seen, followed by a higher peak, reaching a maximum between 50 and 70 years of age, and then decline after those ages (2,4). Some authors stated that this decline is likely to be an artifact due to chance and bias. Elderly patients may be less likely to present themselves to a doctor due to symptoms of CNS tumor, may also be less likely to be referred for CT, or to have a necropsy if they are dead. The diagnostic bias may also be present in the very elderly people (5).

Mortality rates within each European area do not vary much, with the

Address correspondence to:
Tatjana Pekmezović, Institute of epidemiology, School of medicine, Dr Subotića 8, 11000 Belgrade, Yugoslavia

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majority of countries within the range of 4-10/100 000 (6). In the Belgrade population, during the period 1983-1997, age-adjusted mortality rate for primary CNS tumors was 4.8/100 000 (5.6/100 000 for male, and 4/100000 for female population (7). The shape of age-specific incidence curve resembles of the age-specific mortality curve (8). It means that age-specific mortality rates of CNS tumors also increase exponentially with increasing age up to 65 years, and then decline. Riggs suggests that observed biphasic pattern of age-specific mortality rates can be explained by the existence of a primary CNS tumor-susceptible population subset in which the risk of CNS tumor mortality increases exponentially with age and population subset depletion occurs (8).

The primary CNS tumors occur at almost equal rate in both sexes, except meningiomas, which are more frequent in women (2).

In childhood population, incidence rate of CNS tumors very from 2.5/100 000 to >5/100 000, while mortality rate reaches the value of about 1/100 000 (9).

The etiology of primary CNS tumors remains largely unknown. Numerous epidemiological, genetic and other studies have been carried out to clarify the role of environmental and genetic factors in etiology of CNS tumors. Few definite risk factors have been found for these malignancies.

Ionizing radiation was widely regarded as one of established environmental risk factors for CNS tumors for a long period of time, but more recent studies could not confirm this finding. This is in accordance with the fact that doses of ionizing radiation used in today's diagnostics are low so that no association with the primary CNS tumors can be observed (10).

With traditional epidemiologic research designs, few environmental risk factors for malignant brain tumors have been revealed, and although syndromes exist where CNS tumors occur frequently, these explain a small proportion of the overall incidence. Inherited syndromes, such as neurofibromatosis types I and II, tuberous sclerosis, Gorlin syndrome, Turcot syndrome, and nevoid basal-cell carcinoma syndrome are established as being associated with tumors of the CNS. However, they are present in only a small fraction (< 5%) of patients (9).

In a similar way, the search for genetic causes has been thwarted by the rarity of families with multiple affected relatives, inhibiting genetic linkage, sib-pair, or even population-based association studies. In several genetic epidemiologic studies, familial aggregation of CNS tumors was seen. There is an increased risk of cancer in sibs, but the evidence regarding the occurrence of cancer in other relatives is inconsistent.

Molecular genetic studies generally involve searching for candidate proto-oncogenes and tumor suppressor genes by comparing DNA from tumor material with constitutional (germ line) DNA.

Several recent epidemiological studies have investigated relations between CNS tumors and maternal diet. These studies based on hypothesis that transplacental exposure to N-nitroso compounds increases the risk of childhood CNS tumors. Although the evidence is far from being conclusive, they found an increasing risk with increasing frequency of processed meats, particularly for mothers who took no vitamin (10). At the opposite, some recent epidemiological studies provided indication that prenatal vitamin supplementation might be related with reduction of brain tumor risk (11).

Early reports suggest that an association between CNS tumors and residential exposure to electromagnetic fields have not been confirmed. Also, no consistent association between these tumors and inferred parental occupational exposure to electromagnetic fields has been observed (9).

Other suggested risk factors for which the evidence is inconsistent or merits further investigation are previous head injures, family history of epilepsy, high birth weight, maternal passive smoking and use of antiepileptic drugs and barbiturates during pregnancy, etc (10).

Having in mind all mentioned findings relating to frequency, distribution and etiology of primary CNS tumors, prospective regional studies of incidence patterns and up to date epidemiological appraisal are necessary. Also, there is need for current estimation of geographical and secular variation of occurrence of CNS tumors. Further analytic epidemiological investigations are required to confirm associations suggested in the few previous studies and to identify other currently unknown associations.

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Svetozar DAMJANOVIĆ
Milan PETAKOV
Vera POPOVIĆ
Marina NIKOLIĆ-ĐUROVIĆ
Mirjana DOKNIĆ
Dragana GRUDIĆ

INSTITUTE OF ENDOCRINOLOGY, DIABETES & METABOLIC DISEASES, MEDICAL SCHOOL OF BELGRADE, BELGRADE, YUGOSLAVIA

Pituitary adenomas: Clinical significance and genetic syndromes

KEYWORDS: Pituitary Neoplasms; Adenoma; Multiple Endocrine Neoplasia

In the largest neurosurgical series, pituitary tumors represent up to 20% of intracranial neoplasms (1). In these series functioning adenomas are the most frequent (about 60%), while in autopsy series, so called non-functioning pituitary adenomas are more frequent. Incidental adenomas could be found at autopsy in 25% of cases as well (2). An increased risk for cardio- and cerebrovascular mortality is observed in patients with hypopituitarism (3,4). Women seem to be at greater risk than men for cerebrovascular mortality. Independent predictor of increased mortality is pituitary deficiency starting early in the life. Beside this, hypogonadal men with acromegaly are at higher risk for the development of high-output heart failure (5). Mortality from malignant disease in patients with pituitary adenomas remains controversial issue. Women seem to be at grater risk than man in this respect. We have recently shown increased incidence of neoplasia not only in patients with acromegaly but also in patients with clinically non-functioning (NF) pituitary adenomas (6).

Pituitary tumors can be a component of genetic syndromes. Multiple endocrine neoplasia type 1 (MEN1) comprises parathyroid adenomas, eneropancreatic gastrinomas and insulinomas, as well as in 10-50% of these patients pituitary adenomas, most commonly lactotroph adenomas (7). Mutations in tumor-suppressor gene located on chromosome 11q13 are responsible for MEN 1. The product of this gene is menin, which is usually downregulated or truncated in MEN1-associated pituitary adenomas. Linkage analyses have shown that familial non-MEN1 somatotrophinomas are associated with locus 11q13 as well. The G-protein gene GNAS1, or gsp, is mutated in McCune-Allbright syndrome and in a significant subset of isolated somatotrophinomas (8). Carney syndrome is a genetically heterogeneous autosomal dominant disorder mapped to 2p16 and another locus. The goal of this study is to determine the prevalence of hypopituitarism and MEN1 among patients with newly discovered pituitary adenomas.

The study group consisted of 674 consecutive patients with pituitary tumors seen between 1998 and 2002 at the Institute of Endocrinology, Diabetes and Metabolic Diseases, Clinical Center of Serbia, University of Belgrade. Almost 70% of 180 patients with NF pituitary adenoma had growth hormone deficiency. Partial hypopituitarism (deficiency of two pituitary hormones) was found in 42 (23%) of these patients. Deficiency of three or more pituitary hormones was found in 55/I80 (31%) patients. Gonadotrophin deficiency was detected in certain number of patients with acromegaly 48/192 (25%) and panhipopituitarisam in 13 patients (7%). All patients 182 (100%) with prolactinomas had gonadotrophin deficiency. Irreversible GH hyposecretion is frequent in these patients. Panhipopituitarism was discovered in 10 (5%) of patients with prolactinoma. At this moment we do not have data about hypopituitarism among 120 patients with Cushing's disease. Only one patient had non-secretory malignant pituitary tumor.

Ten of all patients had MEN1-associated pituitary tumor. Nine (90%) of these patients had primary hyperparathyroidism as a component of disease. One woman with prolactinoma had bronchial carcinoid tumor and gastrointestinal neuroendocrine tumor in the proximity of papilla of Vater. A female patient with MEN1-associated acromegaly had papillary thyroid carcinoma as well. Neither hyperparathyroidism nor acromegaly was found among members of family, however papillary thyroid carcinoma was found in her son and in one of her cousins. Papillary thyroid carcinoma was associated with MEN1 syndrome (insulinoma with hyperparathyroidism) in a patient without pituitary tumor. Does this association occur by the chance remains to be elucidated.

In conclusion, high frequency of hypopituitarism is found in both patients with non-functional pituitary tumors and patients with acromegaly. Our studies suggest high incidence of other neoplasia in these patients as well. Thus, in spite the low incidence of pituitary tumors in human pathology, these tumors could be useful biological models for the anticipation studies related to other systems.

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Address correspondence to:
Damjanović Svetozar, Institute of Endocrinology, Diabetes & Metabolic Diseases, Medical School of Belgrade, Dr Subotica 13, 11000 Belgrade, Yugoslavia, E-mail: sova@net.yu

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Dubravka CVETKOVIĆ-DOŽIĆ
Slobodan DOŽIĆ
Milica SKENDER-GAZIBARA

INSTITUTE OF PATHOLOGY, MEDICAL FACULTY, UNIVERSITY OF BELGRADE, YUGOSLAVIA

Significance of histopathological and molecular genetics investigations on the diagnosis and prognosis of astrocytic and oligodendroglial glioma

KEYWORDS: Glyoma; Genetics, Biochemical; Prognosis ; Cytological Techniques

INTRODUCTION

Gliomas represent the most common primary brain tumors. Despite their significant incidence their classification and grading remain controversial. For instance, there is a number of grading systems for glioma and the diagnosis of oligodendroglial glioma is highly subjective. To date, classification and grading has relied on histopathological and immunohistochemical findings. However, histological parameters have not explained differences in survival within this tumor group. The possibility of elucidating the molecular basis of glioma formation may impact both on diagnostic and therapeutic aspects of clinical neuro-oncology. The glioma of astrocytic and oligodendroglial type are currently in the focus of molecular genetic analyses.

ASTROCYTIC GLIOMA

Diffuse astrocytic gliomas (low-grade astrocytoma - WHO grade II, anaplastic astrocytoma - WHO grade III and multiform glioblastoma - WHO grade IV) are the most common brain tumors. They have the tendency for malignant progression, with the multiform glioblastoma (GBM) as the most malignant phenotypic endpoint.

Histopathological diagnosis

The histopathological diagnosis of diffuse astrocytic glioma as well as WHO grade are made by applying the 2000 World Health Organization (WHO) criteria (1). These include: cell types (different forms of astrocytes, giant cells, small undifferentiated cells, spindle cells and oligodendroglial cells); cell proliferation assessed by counting mitoses and by determining the fraction of Ki-67/MIB-1 positive nuclei; necrosis (not present, band-like with pseudopalisading, large ischaemic); microvascular proliferation (not present, moderate, extensive/glomeruloid); lymphocytic infiltration; thromboses, sarcomatous growth (not present, predominant - gliosacoma) and expression of GFAP (glial fibrilar acidic protein).

Low-grade astrocytoma is predominantly manifested in young adults. It is characterized by high degree of cellular differentiation, slow growth, diffuse infiltration of neighboring structures and tendency for malignant progression to anaplastic astrocytoma and eventually to secondary glioblastoma. However, the majority of GBM develop de novo (primary GBM) without a recognizable less malignant precursor lesion (2,3). They manifest in older adult patients (mean 55 years) after a short clinical history of usually less than 3 months. Secondary GBM (the terms primary and secondary GBM were first used by Scherer in 1940) occur in younger age group (mean 39 years), show a slightly more favorable outcome and develop far less often than primary GBM. The time interval for progression from diffuse low-grade astrocytoma to secondary GBM varies considerably (mean 4-5 years). In regard to histopathological and immunohistochemical features there are no differences between primary and secondary GBM.

Molecular genetics

Molecular genetics of low-grade astrocytoma (WHO grade II) include point mutations in the p53 tumor suppressor gene. It was shown that the frequency of p53 mutations are very high (50%-80%) in low-grade astrocytomas which progress to GBM. Since approximately 25% of low-grade astrocytoma do not contain p53 mutation, other genetic alterations may be involved. These include loss of heterozygosity (LOH) on chromosomes 10p and 22q (17%) and chromosome 6 deletion (14%). Increased mRNA expression of PDGFRα is observed in astrocytic tumors of all stages, but gene amplification was only detected in a small subset of GBM.

Anaplastic astrocytoma (WHO grade III) has a high frequency of p53 mutations. Additional genetic changes found in some percentage of cases include p16 and p19 deletion, RB alterations, PTEN mutations, CDK4 amplification and LOH on chromosomes 10q (15-30%), 19q (40%), and 22q (30%) (4).

Recent studies have identified distinct molecular alterations in GBM, adding a novel set of parameters for evaluation of clinical course and therapeutic responses (5). The primary GBM are characterized by EGFR amplification (40% of cases) and/or overexpression (60%), CDKN2A, CDK4 and PTEN mutations (30%), RB alteration and p16 deletion (30-40%) (6). There is LOH on the entire chromosome 10 (50-80%) as well as on several chromosomal arms (1p, 9p, 13q, 17p, 19q, 22). The sequence in which gene alterations are acquired is not known since these neoplasms develop very rapidly, without a clinically or histopathologically identifiable precursor lesion (7). The p53 mutations are less common in primary GMB (<10%). Some of these cases have the phenotype of giant cell GBM. MDM2 overexpression/amplification is a genetic hallmark of primary GBM that lack a mutation.

Secondary GBM frequently contain p53 mutations of which >90% are already present in the first biopsy of low grade or anaplastic astrocytoma. Most likely, the p53 mutation is the initial gatekeeper lesion in astrocytic tumor which then, through genetic instability undergoes malignant progression (8). The pathway to secondary glioblastoma is further characterized by LOH on chromosome 17p and 10q (but not on the entire chromosome 10 as seen in primary GBM).

Pilocytic astrocytoma (WHO grade I) represents the most common glioma in children. In contrast to diffuse astrocytoma, this slow growing and circumscribed neoplasm is remarkable in maintaining WHO grade I status over years and even decades. The mutational inactivation of the p53 gene does not play a role in the evolution of this tumor (9).

Association between clinical and histopathological parameters and survival

The favorable parameters for GBM include younger age, good Karnofsky performance, lateral tumor localization, macroscopic complete resection, area of better histopathological differentiation and abundant presence of giant cells (gigantocellular GBM).

Association between molecular parameters and survival

Recent studies indicate that p53 mutations are a favorable prognostic factor independent of primary or secondary GBM. These mutations show the ten-

Address correspondence to:
Dubravka Cvetkovic-Dozic, Institute of Pathology, Medical Faculty, University of Belgrade, Dr Subotica 1, P.O.Box 168, 11000 Belgrade, Yugoslavia, E-mail: dozic@eunet.yu

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dency to occur more frequently in younger than in older GBM patients. This may explain the better survival associated with secondary GBM since these patients frequently combine 2 favorable parameters - younger age and p53 mutations. Some investigator reported that amplification and overexpression of EGFR gene is associated with poor prognosis, while others have not confirmed this finding (10). LOH10q is associated with poorer survival. High levels of expression of PTEN were found to be associated with longer survival. The genomic alterations of LOH1p and LOH19q, which are observed in the majority of oligodendroglioma, are also observed in GBM. However, in contrast to oligodendroglioma, in GBM loss of 19q is more likely to be partial than complete and loss of 1p is uncommon (approx. 10%). It was suggested that combined loss of chromosomal arms 1p and 19q might indicate the better prognosis and potential sensitivity to chemotherapy in GBM patients, while isolated loss of either 1p or 19q is of no prognostic significance. If this were to be confirmed, LOH analyses may allow identification of a subgroup of chemosensitive GBM patients that could not be distinguished by morphologic investigation (11).

OLIGODENDROGLIAL GLIOMA

Oligodendroglial glioma is moderately common brain tumor of adults that generally recur locally. Malignant progression on recurrence is not uncommon, although it is thought to be less frequent than in diffuse astrocytoma. The WHO grading system recognizes two malignancy grades for these neoplasms: WHO grade II for well differentiated and WHO grade III for anaplastic oligodendroglioma.

Histopathological diagnosis

The histopathological diagnosis of oligodendroglial tumors is highly subjective because there are no immunohistochemical markers available for their specific recognition and there are no reliable histological criteria by which well-differentiated oligodendroglioma can be separated from anaplastic examples. Most studies have supported a combination of histological parameters that may be associated with worse prognosis. These include cellular density, nuclear atypia, high mitotic activity, microvascular proliferation and necrosis. Nevertheless, application of these criteria to individual cases often reveals a lack of consistency and reproducibility in classifying oligodendroglial tumor among different observers.

Molecular genetics

Molecular genetic studies have shown that oligodendroglial tumors display distinctive genetic parameters that could provide an objective and reproducible framework for classifying of these neoplasms. The oligodendroglial genetic profile consists of loss of the entire 1p (40%-90%) and 19q (50%-80%) chromosomal arms. Virtually all oligodendogliomas with LOH on 1p have also lost alleles on 19q, a finding that suggests a synergistic effect of both alterations. In contrast to astrocytic tumors LOH on 17p is rare (<10%), as well as the mutations in the p53 gene (10-15%). Besides this, well-differentiated oligodendroglioma has the EGFR and PDGF/PDGFR overexpression. Anaplastic oligodendroglioma shows LOH on several others chromosomes, most frequently 9p and 10q (less commonly) and homozygous deletion of CDKN2 gene. EGFR or CDK4 amplification is restricted to small subsets (<10%) of these neoplasms (12).

Association between clinical and histopathological parameters and survival

Factors associated with more favorable prognosis of oligodendroglioma include younger age, frontal lobe location, complete surgical removal and better histological differentiation. Recent studies have shown that high proliferative activity (Ki-67 labeling indices of higher than 3%) is indicative of a worse prognosis.

Association between molecular parameters and survival

Molecular findings are of great value for prognostic and therapeutic evaluation of oligodendroglioma. Recent studies have indicated markedly improved prognosis of that oligodendroglioma with allelic losses on chromosomal arms 1p and 19q. These losses also may predict favorable response to chemotherapy of anaplastic oligodendroglioma (14).

CONCLUSION

Histopathological evaluation should remain the chief support of brain tumor classification. Nevertheless, molecular genetic studies can play an important part in standardizing tumor categorization and resolving difficult diagnostic problems. These studies can be used to subdivide GBM into biologically distinct subsets and are currently being used to predict therapeutic response and survival in patients with anaplastic oligodendroglioma.

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Milica SKENDER GAZIBARA
Dubravka CVETKOVIĆ DOŽIĆ
Slobodan DOŽIĆ
Vitomir GOVEDAROVIĆ

INSTITUTE OF PATHOLOGY, MEDICAL FACULTY, UNIVERSITY OF BELGRADE, BELGRADE, YUGOSLAVIA

Value of the proliferative and hormonal markers in estimation of biological behaviour of meningioma

KEYWORDS: Meningioma; Immunohistochemistry; Ki-67 Antigen; Steroids

INTRODUCTION

Meningiomas are common (13-26% of all primary intracranial neoplasms), usually benign slow-growing neoplasms of the central nervous system (1). However, some meningiomas can display aggressive behavior characterized by invasion of the brain, dura, and adjacent bone, multiple recurrences and a fatal outcome. While, the majority of meningiomas have distinctive morphologic features that permit reliable diagnosis and classification (WHO grade I - benign, grade II - atypical and grade III - malignant s. anaplastic) by conventional histologic technique, some variants of meningioma, however, may raise the problems in assessing their prognosis. Although histological features may indicate the malignant nature of the neoplasm, they do not always correlate with patient outcome, since 2.3% to 30% of histologically benign meningiomas recur following macroscopically complete surgical removal (2). Recurrence is often accompanied by a more aggressive profile of histopathology and biologic activity. High mitotic index has been generally considered to be a strong indicator for tumor recurrence, but even this claim has been challenged (1). The risk of recurrence in the individual patient and the biological behavior of meningiomas can not be predicted by histology alone. In efforts to identify tumors with more aggressive clinical behavior, a number of authors have investigated the association of meningioma recurrence with histological features, as well as with data obtained from a variety of techniques which have been developed to evaluate cell proliferation (3,4). Hormonal (presumably progesterone) receptor status has also been correlated with recurrence of meningioma (5).

In this paper we want to indicate the present opinion about impact of proliferative and hormonal markers in estimation of biological behavior of meningiomas.

PROLIFERATIVE MARKERS

In an attempt to determine more precisely the correlates of aggressiveness and growth of meningiomas, researches have developed quantitative methods of measuring the proliferative activity (kinetics) of meningioma cells including: thymidine labeling, bromodeoxyuridine incorporation, nuclear organizing region analysis, histone in situ hybridization, telomerase activity, flow cytometric analysis and immunohistochemical markers. Among these techniques, immunohistochemical based markers such as PCNA and Ki-67/MIB-1 are widely used, because they are relatively easy to perform, they are fairly inexpensive and can be performed in a reasonably short period of time (3). Ki-67 antibody is more sensitive cell proliferation marker than PCNA. The antigen associated with Ki-67 antibody is encoded by a gene situated on chromosome 10. The antigen is present in the nuclei of cells in the G1, S, G2 and M-phases of the cell cycle, while, resting cells in the G0 phase do not express the Ki-67 antigen. By convention, and similar to mitosis counting, counts are usually performed in the area with the strongest immunostaining. The Ki-67 proliferation or labeling index (LI) is defined as the percentage of positively immuno-reactive tumor cell nuclei. This method (as well as mitosis counting) is subject to limitations associated with tumor heterogeneity and interobserver variability. The most authors reported that the distribution of the Ki-67 positive cells is heterogeneous in high-grade tumors, while, a more diffuse pattern is usually described in low-grade meningiomas (5).

There are significant increasing values of Ki-67 LI between tumor grades, from benign (mean 3.8% $\pm$ 3.1), over atypical (mean 7.2% $\pm$ 5.8) to anaplastic meningiomas (mean 14.7% $\pm$ 9.8). Differences in the mean Ki-67 LI between groups are statistically significant. However, Ki-67 LI, may vary considerably among anaplastic meningiomas (1.3 - 24.2%) (1), and there is also some overlap in Ki-67 LI ranges between different groups (6), which is important for interpretation of an individual Ki-67 LI in a given tumor. This interpretation must be done with caution, because a low Ki-67 LI does not necessarily imply a tumor without aggressive potential. The low LI may represent a sampling phenomenon. Evaluation of Ki-67 antibody is particularly helpful in cases that are histologically graded as "borderline". In these cases, high labeling index may suggest that the meningioma may be potentially more aggressive in terms of behavior (3). On other side, some authors believe that Ki-67 antibodies have no advantage over counting mitoses to assess proliferate activity in meningioma (6). Mitotic activity is included as a criterion of malignancy in the latest WHO version for meningioma grading (1).

HORMONAL MARKERS

During the last two decades much attention has been paid in the literature to the endocrine influence on meningiomas. This is supported by their higher incidence in women and the facts that meningiomas may wax and wane with pregnancy, and that they are positively associated with breast cancer. These observations opened the door to investigation of the role of sex hormone receptors in the growth of meningiomas and to a greater understanding of the pathways that control the expression and function of these receptors (7).

Approximately two-thirds of meningiomas express progesterone receptors (PR), with a higher fraction in meningiomas from female patients (7). It is unknown, however, how PR expression is regulated, especially since estrogen receptors (ER) are virtually absent in these tumors.

Although PR status was recently suggested to be an independent prognostic variable (5), this marker is also closely linked with histological grade. Expression of PR is associated with benign histology. Progesterone receptors are more frequently detected in meningothelial meningiomas than in other types, especially the atypical or malignant meningiomas (1). Atypical or anaplastic tumors frequently lack progesterone receptors (8). Progesterone receptor-negative meningiomas tend to be larger than progesterone-receptor-positive tumors.

Some recent data indicate that clinical factors, such as age, sex, tumor location and menopausal status, do not seem to correlate with progesterone receptor status (7). Progesterone receptor status has also been correlated with recurrence. Absence of progesterone receptors in meningiomas, together with a mitotic index greater than 6/10 high power fields, and malignant tumor grade, are a highly significant predictor for shorter disease-free inter-

Address correspondence to:
Milica Skender Gazibara, Institute of Pathology, Dr Subotića 1/I, 11000 Belgrade, Yugoslavia,
E-mail: mgazibar@eunet.yu

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vals in meningiomas and poor outcome.

CONCLUSION

Although the proliferative markers and hormonal (progesterone) receptor status of meningiomas seem to provide useful, convenient, and predictive criterions for the subsequent evolution of the tumor, they should be used only in combination with other established histopatological features of tumor malignancy (cellular density, nuclear pleomorphism, nucleolar prominence, mitosis and necrosis - especially multifocal micronecrosis). A simple, reproducible clear set of criteria for the tendency of a meningioma to recur is yet to be determined. In the last few years there are some new data concerning genetic characterization of meningiomas (9) and some cellular proteins (p53, p21, p27) (10) in meningioma cells which may be valuable in precisely discriminating atypical meningiomas from benign or anaplastic meningiomas, at least in histologically borderline cases.

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Tatjana STOŠIĆ-OPINĆAL
Vesna PERIĆ
Mihail GAVRILOV
Svetlana GAVRILOVIĆ

CENTER FOR MAGNETIC RESONANCE, CLINICAL CENTER OF SERBIA

Fluid-attenuated inversion-recovery MR sequence in the evaluation of low-grade astrocytomas

KEYWORDS: Astrocytoma; Magnetic Resonance Imaging

INTRODUCTION

Low-grade astrocytomas are a heterogeneous group of intrinsic central nervous system neoplasms that share certain similarities in their clinical presentation, radiologic appearance, prognosis and treatment. These tumors are slow growing and patients survive much longer than those with high-grade gliomas do. According to the World Health Organization scheme, these tumors are grades I and II based on the histopathologic evaluation of surgical specimens. Therapeutic approaches for these tumors differ considerably according to grade, including partial or total resection or biopsy to make a histological diagnosis prior to consideration of radiotherapy (1,2). The development of neuroimaging techniques, which allow accurate determination of the grade, helps in better treatment planning and management.

MRI is an important in diagnosis, therapy planning and follow-up of cerebral tumors. It provides excellent detail, both of the anatomy of the lesion and often of its pathophysiology. Pathological features detectable by MRI include presence of cysts, necrosis, hemorrhage, edema and blood-barrier disruption. Follow-up of tumors conventionally involves T2-weighted (T2W), proton density-weighted (PD) and T1-weighted (T1W) imaging, before and after intravenous contrast medium. Typically, on T1W sequences, low-grade astrocytomas demonstrate same or decreased signal comparing to surrounding brain. On T2W sequences higher signal reflects both the tumor and surrounding edema. T2W sequences are widely accepted as the most sensitive MR sequence for detection and delineation of glioma. Whilst these tumors do not usually enhance initially, progression to a higher grade tumor is often accompanied by the appearance of focal areas of enhancement (3).

CHARACTERISTICS OF FLUID-ATTENUATED INVERSION-RECOVERY MRI SEQUENCE

Fluid-attenuated inversion-recovery (FLAIR) MRI sequence is one of inversion-recovery sequences that are used in diagnosis of many pathologi-

Address correspondence to:
Tatjana Stošić-Opinćal, Center for Magnetic Resonance, Clinic Center for Serbia, Pasterova 2, 11000 Belgrade, Yugoslavia, E-mail: tanja.stosic@kcs.ac.yu

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cal conditions including demyelinating diseases, trauma, infections, congenital abnormalities, metabolic and toxic injuries, metastatic tumors, subarachnoid hemorrhage (4,5,6). This sequence is especially useful in the evaluation of white matter abnormalities, particularly in the region around ventricles and around the basal cisterns, as well as those primarily located in cortex, subcortical white matter and brain stem. Considering these localizations, artifacts are often seen. These artifacts restrain assessment of tumor volume and its delineation from surrounding tissue (6). Using FLAIR sequences, T2W images are acquired in which the free water signal is suppressed. Therefore, free water is presented with low signal, while other tissues with a long T2 relaxation time are presented with a higher signal. Setting inversion time (TI) to the signal zero crossing of T1 recovery curve can eliminate the signal from a CSF. Initially, use of FLAIR sequence was limited by a long acquisition time, so the examination lasted too long. However, by combining fast spin echo (SE) and inversion-recovery (IR) sequences, i.e. fast or "turbo" FLAIR, more acceptable acquisition times are achievable (4,7,8).

APPLICABILITY OF FLAIR SEQUENCE IN THE DIAGNOSIS OF LOW-GRADE ASTROCYTOMAS

Flair was found to be better for detection of the lesion and for definition of its margins in comparison with T2W se and PD sequences (6). Comparing with surrounding white matter, tumors on FLAIR images are isointense or hyperintense. Because of the suppression of CSF signal, contrast between tumor and CSF can be greatly increased which gives clearer and more accurate delineation of lesions located near the border of the CSF (Figure 1).

FLAIR is also more applicable for showing different tumor components, especially in regions that are complicated to demonstrate in some planes, such as the vertex in axial imaging. Gray matter signal changes on the border with subarachnoid space are demonstrated well on FLAIR. This is especially important in areas where partial-volume artifact can lead to inaccurate assessment of lesions, such as on coronal images of the frontal, temporal and occipital poles.

FLAIR has shown either equal or better sensitivity in detecting and follow-up of residual and recurrent tumors, especially low-grade astrocytoma (8). Follow-up of tumor margins is especially important in early detection of postoperative relapses. It also defines the postoperative cavity and shows the least amount of susceptibility effect associated with surgical clips. FLAIR well demonstrates local spread to white matter. The surgical cavity is better defined on FLAIR images with improved display of altered signal in adjacent brain. When there is no cavity, the advantage of FLAIR in defining a tumor lesion is not that clear. Different parts of the lesion can be assessed, such as cystic components, necrosis, peritumoral signal change and solid tumor mass. Signal from calcification has been noted to be lower with FLAIR than on conventional SE images. Subependymal spread is more noticeable on FLAIR due to the absence of artifact effects with CSF and much better contrast (7,8). Contrast-enhanced T1W images should avoid problem of the high signal often seen along the ventricle walls, which can obscure subependymal spread. Artifacts frequently noted on FLAIR images are usually due to CSF flow motion near the foramen of Monro, fourth ventricle and aqueduct. In conclusion, even though FLAIR images are commonly considerate as T2W images with dark CSF, they have mild T1 contrast, which accounts for the ability to see contrast enhancement (CE) (5,7,8). Gadolinium enhancement on FLAIR images may be difficult to see in lesions such as intraparenchymal tumors that have long T2, which makes them hyperintense. In these cases, CE T1W imaging is superior to postcontrast fast FLAIR imaging for detecting the breakdown of the blood-brain barrier (9,10).

CONCLUSION

FLAIR is currently used for supplementing basic MRI protocols. FLAIR technique may be used as an adjunct to T2W or PD SE imaging and may even replace PD imaging. FLAIR is superior for appreciation of the lesion and for demonstration of its margin. However, peritumoral edema is clearly demonstrated, and the FLAIR images often delineate edema from tumor, and distinguish CSF from a cystic or necrotic component, better than T2W and PD images. In cases when tumor has a cystic or necrotic component, the signal intensities of such areas are different from that of CSF on FLAIR images. FLAIR demonstrates better local spread of the tumor than T2W and PD images.

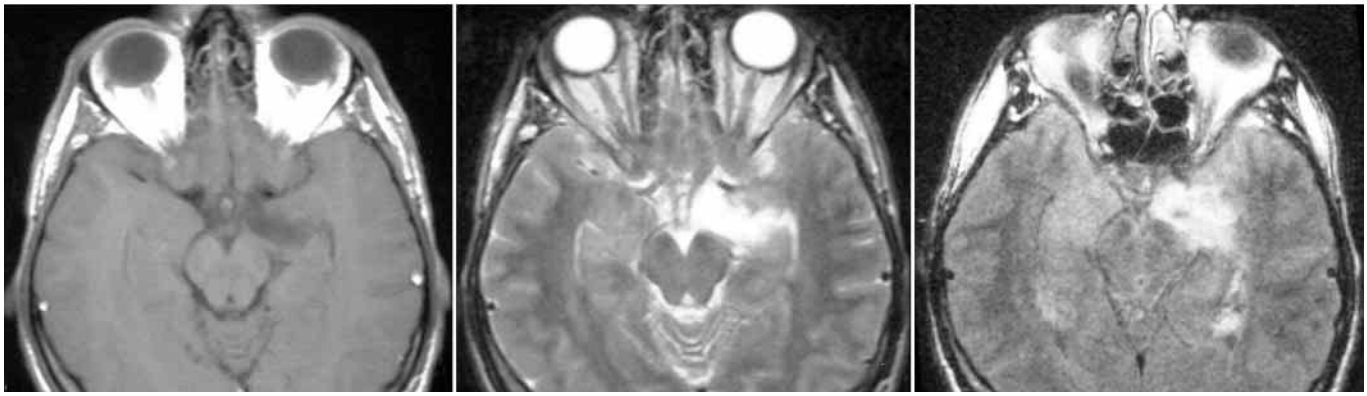

Figure 1. (a) Axial contrast-enhanced T1W, (b) T2W SE, (c) FLAIR imaging from a 33-years old patient with histologicaly approved low-grade astrocytoma. FLAIR (c) better demonstrates local spread of the tumor

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Danica GRUJIČIĆ
Branislav JEREMIĆ
Miroslav SAMARDŽIĆ

INSTITUTE OF NEUROSURGERY, CLINICAL CENTER OF SERBIA, BELGRADE, YUGOSLAVIA

Contemporary management of low grade intracerebral gliomas

KEYWORDS: Glioma; Surgery; Radiotherapy

INTRODUCTION

Tumors of neuroglial cells represent nearly 50% of all primary central nervous system tumors. Among them low-grade gliomas (LGgl) comprise about 25 to 35% of these neoplasms (1). This group of tumors is characterized by numerous histological subtypes, which include: ordinary low grade astrocytomas - LGAs (WHO grade II) with its variants (fibrillary, protoplasmic and gemistocytic), pilocytic astrocytoma (WHO grade I), pleomorphic xanthoastrocytoma (WHO grade II), subependymal giant cell astrocytoma (WHO grade I) usually associated with tuberous sclerosis, oligodendroglioma - LGO (WHO grade II), mixed gliomas like oligoastrocytomas - LGOAs (WHO grade II), ependymoma (WHO grade II) with its variants (cellular, papillary, clear cell), subependymoma (WHO grade I), gangliocytoma (WHO grade I), ganglioglioma (WHO grade I or II), dysembryoplastic neuroepithelial tumor (WHO grade I), desmoplastic infantile ganglioglioma (WHO grade I).

Some forms of low-grade gliomas are indolent hamartomatous lesions (especially those of WHO grade I) with a low proliferative activity, small growth potential, and very little ability for malignant transformation. They can often be controlled by radical or subtotal resection alone.

More challenging for management choice is the group of tumors of WHO grade II, especially low grade astrocytomas, oligodendrogliomas and mixed oligoastrocytomas, to which we put our attention. The behavior of ependymomas differs from that of the other gliomas because of their additional potential to spread through cerebrospinal fluid and not only locally, so we will not discuss their management now.

There are several controversies in the management of LGgl: Radical resection vs. stereotactic biopsy sampling? Radiotherapy (Is it effective? Which dose is ideal? Which method should be used? What treatment field?); Radiosurgery (does it have any role in the treatment of these lesions?); Chemotherapy (Is it appropriate? Which drugs are effective? What treatment regimens or combinations are appropriate?) Is metabolic imaging useful in follow up and treatment decisions? (2)

CLINICAL BEHAVIOR OF LGgl

One of the greatest obstacles to treating LGgl is the inability to define accurately their natural history despite of many reported studies. These tumors are frequently quiescent for a long period prior to diagnosis, so it is very difficult to gain a clear picture of their clinical behavior after the establishment of diagnosis. Sometimes, even symptomatic, these tumors can have a prolonged period of latency with little or no growth.

LGgl affect the brain by two main mechanisms - infiltrating the normal brain tissue by tumor cells, and raising intracranial pressure due to space - occupying effect. For LGgl epilepsy or seizure is by far the most common presenting symptom or sign at the time of diagnosis in 40%-78% of patients (3). Aside from that, all other symptoms and signs like headaches, motor or speech difficulties, visual impairment, cognitive decline, etc can be present at the time of diagnosis. Patients in the past have been typically presented with a high proportion of compressive symptoms and increased intracranial pressure. Nowadays, patients are generally diagnosed much earlier after having only one episode of altered consciousness (4), so only a minority of them have significant functional limitations at the time of presentation. Thus clinicians (especially neurosurgeons and radiotherapist) bear additional responsibility of causing potential harm to an intact patient.

It is obvious that these tumors will eventually progress to the point where they will require treatment. However, the time needed to reach this symptomatic threshold remains unknown. Some of these tumors will become more malignant over time (Apuzzo, 1995), but again, we do not know how long it will take till they change their biological potentials.

DIAGNOSIS OF LGgl

With introduction of computerized tomography (CT) and magnetic resonance imaging (MRI) the diagnosis of LGgl became more accurate and specific and make it possible to perform expecting observation of these patients especially when tumors are located near or in the eloquent brain zones. LGAs are usually hypodense on CT, and hypointense on T1W images on MRI. Contrast enhancement is usually associated with higher grade of tumor malignancy, or worse prognosis and sooner recurrence. LGO are usually partially calcified on CT, and mixed gliomas may have characteristics of both astrocytomas and oligodendrogliomas.

TREATMENT OPTIONS FOR LGgl

The treatment modality will depend on patient's symptoms. There is in no doubt that there must be some kind of intervention when there are signs of raised intracranial pressure or in cases of rapid development of progressive neurological deficit. Radical surgery in these cases will be the treatment of choice.

However, patients with only seizures and minimum symptoms have more than one treatment options. It depends mostly on the location of the tumor (eloquent cortex, deep structures, and cerebrospinal fluid obstruction), general condition of the patient, and the potential harm of surgery.

Therapeutic possibilities usually are (1):

1. Expectant observation only based on imaging diagnosis of LG astrocytoma or oligodendroglioma.
2. Biopsy with confirmation of LGgl and then observation only.
3. Biopsy with confirmation of LGgl and then surgical resection only.
4. Biopsy with confirmation of LGgl and then external beam irradiation only.
5. Biopsy followed by surgical resection and irradiation.
6. Primary surgical resection of suspected LGgl only.
7. Primary surgical resection followed by irradiation.
8. Empirical irradiation of suspected LGgl on basis of imaging diagnosis.
9. Biopsy with confirmation of LGgl and interstitial brachytherapy.

Each of these options has been used by different brain tumor centers worldwide with varying degree of success.

Since there is proved possibility for progression of LGgl into higher pathological grades one must be very cautious with expectant observation only. Repeated MRI or CT should be performed on two to three months, thus following and defining any change in tumor presentation. When confirmation of the LGgl is established then observation might be one of the reasonable

Address correspondence to:
Danica Grujičić, Institute of Neurosurgery, Clinical Center of Serbia, Višegradska 26, 11000 Belgrade, Yugoslavia, E-mail: gruj@infosky.net

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options, especially in older patients with unfavorable location of tumor (basal ganglia, deep white matter, primary motor cortex).

Considering stereotactic or open biopsy in certain number of patients the first one has certain advantages. The craniectomy is small one, there is no need for general anesthesia, and procedure is relatively simple. However, one must always be concerned with a sampling error in tumors that contain areas of different degrees of malignancy. To overlook this disadvantage it is necessary to define different trajectories and targets in tumor bed. According to some large series of patients (5), the surgical morbidity with this method is less than 1%, and diagnostic accuracy is as high as 94% (6).

Despite the continuing controversy over its benefits a large proportion of tertiary brain tumor referral centers presently advocate a radical or near-total resection whenever possible for patients with LGgl. As the residual tumor cells are suspected of having an increased propensity to undergo further malignant transformations most surgeons consider it prudent to attempt a "gross total" removal of the lesion to limit further spread and future recurrence. It is also thought that an initial cytoreduction optimizes subsequent adjuvant therapy by removing central ischemic tumor areas that are "protected" from effects of irradiation or chemotherapy (7). Several large retrospective studies that have analyzed the influence of the degree of surgical resection on long term survival proved that radical surgical resection of LGgl correlated with longer survival (1). However, comparing biopsy with irradiation vs. surgical resection and irradiation this correlation becomes less evident.

As with all surgery, cautious preoperative evaluation and management is essential in minimizing operative-related complications. Surgical approaches depend on location of tumor and all attempts should be made to minimize brain retraction. Surgical morbidity usually does not exceed 10%, but for patients who are intact prior to surgery even a 5-8% chance of impairment can be unacceptable. As there is not clear-cut evidence in support of radical debulking conservative resection for lesions that are adjacent to or within eloquent neural parenchyma has been advocated.

Even after the most aggressive "gross total" resections it is now widely accepted that there will still be as significant number of LGgl cells left behind. Is not surprising that radiotherapy has widely been employed in the management of LGgls. The goals of external beam irradiation and chemotherapy are local control, decreasing recurrence and preventing malignant transformation. However, the effects of irradiation on the natural history of treated LGgl is even more controversial, although many retrospective series prove higher survival rate in 5 and 10 year periods in irradiated patients (8).

It is now recognized that for some types of LGgl (fibrillary and protoplasmic astrocytomas and oligodendrogliomas) after total or subtotal surgical resection radiation therapy can be postponed until disease progression. However, in incompletely resected low grade gliomas the optimal timing of postoperative radiotherapy is an unsettled issue. Several studies indicated an advantage for immediate postoperative radiotherapy (8). Appropriate clinical target volume for irradiation should include the MRI- indicated extent of tumor with a 2 to 3 cm margin of surrounding brain tissue with respect to anatomical boundaries. Hyperfractionated radiation may be of some benefit for these patients (9).

Patients too frail to have surgery should probably undergo radiation for lack of any other treatment options. High dose greater than 60 Gy should be avoided to prevent secondary complications of the radiation itself. Modern techniques of radiotherapy may be associated with decreased toxicity to surrounding brain.

Several studies showed different behavior and outcomes of various histological subtypes of LGgl with better overall survival for oligodendrogliomas and mixed oligoastrocytomas than those with ordinary low grade astrocytomas did.

PROGNOSTIC FACTORS

There are some proven prognostic factors that influence outcome in patients with LGgl. Favorable ones are: age of less than 40 years, seizures as presenting problem, circumscribed lesion on CT and MRI, non-enhanced or homogenous enhanced images, normal functional status, hypometabolism on positron emission tomography (PET), and microcystic with normal vascular pattern. Unfavorable factors are: age of more than 40 years, signs of increased intracranial pressure, diffuse or multifocal lesions, heterogeneous enhancement with contrast medium, functional status impaired, hypermetabolism on PET, gemistocytic variant, and microvascular proliferation (2).

OUTCOME

Treatment failure for LGgl is their tendency to recur locally despite different therapeutic regimens, sometimes even at a higher histologic and clinical grade. Tumor recurrences are diagnosed on the basis of radiographic evidences, even before clinical deterioration. Recurrent LGgl have a 45%-88% likelihood of malignant dedifferentiation at second look. With modern therapeutic regimens there is an overall improvement in survival for those patients. Several retrospective studies with patient group from 1970 to 1997 showed median survival of about 100 months and ten year survival rate of 50-70% (1).

PERSPECTIVES

In the last decade the majority of oligodendrogliomas have been noted to be chemosensitive, both high- and low-grade (10). Today, this treatment represents an alternative to surgery and radiotherapy for recurrent LGOs. Drugs that have been used are procarbazine, CCNU and vincristin in combination.

With further achievements in molecular biology and immunology gene therapy and immunotherapy probably will become one of the alternatives for surgery and irradiation therapy in low-grade gliomas.

CONCLUSIONS

Total or subtotal surgical resection is the therapy of choice for most intracerebral LGgls. It should be performed whenever possible. After postoperative MRI and PET, it should be decided about immediate postoperativne radiotherapy. If there are the signs of the tumor rest, radiotherapy is essential. Patients in poor clinical grade, or deep seated tumors should undergo stereotactic biopsy followed by stereotactic radiosurgery, or conventional radiation therapy. In recurrent diseases any kind of surgery should be followed by radiation therapy, or/and chemotherapy for chemosensitive oligodendrogliomas. Accurate histopathological diagnosis is essential for treatment choice and prognosis.

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Ivana GOLUBIČIĆ
Marina NIKITOVIĆ
Gordana GLIGORIJEVIĆ

INSTITUTE FOR ONCOLOGY AND RADIOLOGY OF SERBIA, BELGRADE, YUGOSLAVIA

Quality control in radiotherapy of brain tumors

KEYWORDS: Quality Control; Radiotherapy; Brain neoplasms

SYSTEM OF QUALITY CONTROL

The idea of quality control and quality assurance was first introduced into industry, including all necessary planned and accepted procedures, providing precise and permanent functioning of the system, according to accepted standards. Quality control program was introduced into medicine in 1976 on suggestion of the World Health Organization - WHO. The basic aim was the control of accepted treatment programs, their improvement and optimization to enable proper and high quality treatment of patients.

Acceptance and quality control realization should make possible that chances for cure of patients of the same stage and type of disease do not depend on the place and team conducting the therapy. Also, treatment planned in this way should provide designing of methods of treatment and adequate equipment, which are safe both for patients and the staff as well (1).

In recent decades, radiotherapy is rapidly developing not only because of the introduction of new, contemporary technologies, but also because of the most modern approach in development of the quality control system. General quality control system is introduced, covering all aspects during treatment process, from the time of presentation, diagnosis, histological finding, treatment to follow-up of patients. It is about complex quality control system, which includes clinical, physical and technical aspects of quality control. Clinical aspects include basic data on patient, disease type, staging and planned treatment according to accepted therapeutic protocols, treatment results and continual patients' follow-up after completion of treatment. Physical aspects include available equipment, dosimetry, isodose distribution planned to dosimetric protocols and both international and local regulations and technical aspects comprise precision of application of the planned therapeutic program - positioning of a patient and irradiation beam, checking of geometric parameters and the beam modifiers, protection precision (2,3,4). For the purpose of follow-up of applied regulations and comparison of results standardization has been made and acceptance of the international recommendations for planning, conducting and control of therapeutic programs - ISO 9000, ICRU Report 50, ICRU Report 62, Quality Assurance in radiotherapy program (5,6,7).

CLINICAL ASPECTS OF QUALITY CONTROL

Primary brain tumors are the most frequent solid tumors in children with 20% of all malignant diseases in childhood, while the incidence in adults is low (1.5%).

Nevertheless, the importance of quality control in radiotherapy is essential both in children and in adults, regarding risk for late sequelae, as well as possible physical, neurological and cognitive deficits with unsatisfied quality of life.

Whenever possible, radical tumor dose should be applied in radiotherapeutic treatment of the central nervous system tumor. Determination of irradiation fields is conditioned by histopathological type of the tumor and malignancy grade. Applied irradiation dose also depends on the age, histopathological type, malignancy grade and extension of the surgical procedure. The most frequently applied irradiation technique are cranial and craniospinal technique, requiring precision in planning and conducting of the program of irradiation technique (8). Cranial irradiation should include whole brain or, more often local techniques with different safety areas depending on the tumor type. These irradiation techniques are also applied in some stages of acute limphoblastic leukemia, as well as in adults.

PHYSICAL ASPECTS OF QUALITY CONTROL

Physical aspect of quality control comprises available equipment, dosimetric determination of the beam quality parameters, absorbed dose, isodose planning according to dosimetry protocols and both international and local regulations (9). In order to use a certain radiotherapeutic device in every day use for treating patients, it should function correctly and according to producer's recommendations and have stable determined physical characteristics of the irradiation beam. Both these aspects are mutually conditioned and connected, having common aim - to enable daily precise application of the planned therapeutic dose.

Quality control aspect in cranial and craniospinal radiotherapy is especially important for follow-up of effects at the field separation level. Problem of the field separation has been known for long time in the radiotherapy planning. The aim in radiotherapy is to achieve dose uniformity at separation level, making adequate choice of the irradiation technique, dose distribution, and precisely giving irradiation treatment.

In craniospinal radiotherapy this refers to separation between cranial and spinal fields, and separation of the spinal fields. Many authors have analyzed this problem and tried to find optimal solution that will satisfy all required demands. Numerous studies have shown that any deviation from stated separation intensifies effect of overdosing or underdosing in the function of separation area and intensity.

TECHNICAL ASPECTS OF QUALITY CONTROL

Technical aspects of quality control refers to correct functioning of radiotherapeutic megavoltage machines, and correct conducting of all procedures related to immediate realization of radiotherapeutic treatment (10). In cranial and craniospinal radiotherapy this, in the first place, refers to checking of reproducibility of patient's positioning to irradiation plan, positioning of the fields and fields' angle, then distance control, protecting blocks, compensators, wedge filters and equipment for immobilization during the treatment.

Optimal application of the physical and technical parameters control program provides permanent control and confirmation of dosimetry stability of the radiotherapy machine, what, with control clinical parameters enables adequate planning and application of the therapeutic plan of treatment.

All three aspects of quality control are mutually connected and have common aim to provide correct, reproducible irradiation with planed total tumor doses according to intracranial localization, histological type and grade, age and performance status.

CRANIAL RADIOTHERAPY

Aim of the cranial irradiation is whole brain irradiation, with or without irradiation of complete intracranial subarachnoid space. For the first option target volume must include subarachnoid space around optical nerve, what

Address correspondence to:
Ivana Golubicic-Magazinovic, Institute for Oncology and Radiology of Serbia, Pasterova 14, 11000 Belgrade, Yugoslavia, E-mail: ivanagm@ncrc.ac.yu

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practically means inclusion of orbit top. Also, the fields must include cribriform plate and temporal pit. Hypodosing of the cribriform region has been considered the most common cause of the supratentorial relapse in the patients with meduloblastoma. Lower limit of the field is at the level of the second cervical vertebra in order to provide homogeneous distribution at the level of peripherally localized subarachnoid space. Apart from application in the patients with certain primary brain tumors and brain metastases, this technique is applied in high-risk stages of acute limphoblastic leukemia, which means prophylactic or therapeutic teleradiotherapy in neuroleukemia.

Cranial radiotherapy using local techniques is indicated in astrocytoma, oligodendroglioma, ganglioglioma, hemangioblastoma, some benign tumors and vascular malformations as well. Safety margins include borders of radiation fields 2cm out of macroscopic tumor on imaging findings (CT, MRI) in low-grade gliomas, but 5-7cm in high-grade gliomas.

CRANIOSPINAL RADIOTHERAPY

Craniospinal technique is necessary for majority of pediatric brain tumors that have tendency of dissemination through liquor - supratentorial PNET, meduloblastoma, infratentorial and high-grade supratentorial ependymomas, germ cell tumors, pinealoblastoma, horioid plexus carcinoma. Aim is to irradiate complete subarachnoid space, both cranial and spinal one. Cranial field corresponds to previously described and spinal should include spinal cord up to S2 vertebra. Cranium and proximal part of cervical cord up to C4 vertebra are irradiated from two opposite parallel fields using wedge filters in many centers, including our Institute as well. Vertebral axis is irradiated with one or more direct fields. Lower edge of the spinal field is planed on the basis of MRI examination, as well as lower edge of S2, or lower level of tecal bag. Dose is focused on front surface of C7 and L5 vertebral bodies. Quality control algorithm applied at all levels of planned cranial and craniospinal radiotherapy has been accepted in contemporary radiotherapy approach. After precise defining of target volume, in accordance to the international recommendations, the field localization is determined on a patient - simulation and immobilization, according to isodose plan. Then start irradiation treatment and the first positioning with "checking" film - gammagraph on the therapy machine. Quality control should be necessarily one during irradiation treatment, in relation to all relevant technical parameters of the quality control: fields positioning with the cranial field precision control, protection checking of critical locations (eyes, cribriform plate, temporal pits), precision of craniospinal and spinal crossing . Then, control of patient's positioning, checking of geometric parameters, beam modifiers and planned protections. Planned radiotherapy program is individually conducted for every patient, in accordance with accepted and already mentioned internationals regulations and recommendations in radiotherapy.

ABSORBED TUMOR DOSE AND FRACTIONATION SCHEDULE

For the majority of pediatric brain tumors conventional fractionation is recommended with daily doses from 1.8 to 2.0Gy and total absorbed dose of 50 to 55Gy. Prophylactic doses in craniospinal technique are from 30Gy to 40Gy, daily fractions are about 1.5Gy. All irradiation fields are given every day, five days per week. There are a few schedules for brain tumors in adults. For patients with minimal neurological deficits and satisfied performance status teleradiotherapy used to be conventional with radical total doses range 55-60Gy, or hypofractionated with 30Gy in 10 fractions. On the other hand, hypofractionated regimens such as 18Gy in three fractions or 12Gy in two fractions or 20Gy in five fraction are recommended particularly for patients with neurological deficits, bad performance status and minimal expectance for longer survival.

CONCLUSION

Radiotherapy techniques for brain tumors are complex and require precision in planning and giving radiotherapy programs. Continual application of quality control should enable achieving better treatment results with minimizing risk for late treatment-related complications. Introduction of uniform and precise parameters for the therapy planning, dose determining and patient's control, makes possible for optimal follow-up and comparison of treatment results between different therapeutic centers.

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