AJPMHS GLOBAL RESEARCH NETWORK

AMERICAN Journal of Pediatric Medicine and Health Sciences
Volume 3, Issue 12, 2025 ISSN (E): 2993-2149

Glial Tumors of the Brain: General Principles of Diagnosis and Treatment

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Abstract: Gliomas are the most common primary tumors of the central nervous system and represent a major medical and socio-economic problem due to their high incidence, malignant potential, and unfavorable prognosis. They account for up to 40–45% of all intracranial neoplasms and predominantly affect individuals of working age. Gliomas are characterized by infiltrative growth, absence of clear anatomical boundaries, high recurrence rates, and pronounced angiogenesis, especially in high-grade forms. This review summarizes current concepts of glioma classification based on tumor localization, histogenesis, and degree of malignancy according to the World Health Organization criteria. Modern diagnostic approaches, including advanced neuroimaging techniques, as well as contemporary surgical, radiotherapeutic, and chemotherapeutic treatment strategies, are discussed. Particular attention is paid to intraoperative technologies aimed at increasing the radicality and safety of tumor resection. Despite ongoing progress, the treatment of gliomas remains limited in effectiveness, highlighting the need for further research and development of novel therapeutic approaches in neuro-oncology.

Keywords: glioma, brain tumors, neuro-oncology, WHO classification, neurosurgery, radiotherapy, chemotherapy.

Introduction. Cerebral glial tumors continue to be a relevant issue of contemporary medicine in spite of considerable breakthroughs in oncology and neurosurgery. Cerebral gliomas constitute about 40–45 % of all glial tumors' general structure; these tumors are mostly diagnosed at the age of 30–60 thus affecting the most able-bodied segment of population. Glial tumors usually arise out of astrocytal or oligodendrocytal cell population and are characteristic of high growth rate, invasiveness, early metastatic ability, high rate of recurrence and unfavorable prognosis. The present paper focuses at the contemporary clinical classification of gliomas based upon their location, histogenesis and activity of growth. Invasive growth with absence of distinct macroscopic border between the tumor and normal brain tissue is a characteristic peculiarity of glial brain tumors. This type of growth is peculiar for fast-growing highly malignant gliomas (anaplastic astrocytomas, glioblastomas). It is characteristic of unfavorable outcome. Anaplastic gliomas like a majority of malignant tumors are characteristic of intensive development of pathologic vascular network which boosts the rate of tumor growth as well as the intensity of metastases-forming also increasing the risk of cerebral hemorrhage into the tumor. Nodal type of growth with distinct border and moderate infiltration is less typical and may be found in case of conditionally benign gliomas with more favorable prognosis. The paper gives a detailed review

of basic surgical, radiological and chemotherapeutical approaches towards treatment of gliomas. Closing the review the authors conclude that methods described in the paper do not exhaust all suggested improvements of glial tumors treatment and that elaboration of novel methods will bring neurooncologists closer to solving this actual problem. Gliomas (neuroectodermal, neuroepithelial tumors) are primary tumors of the central nervous system that initially arise from glial cells forming the brain parenchyma. Current interest in the problem of glial brain tumors is обусловлено by two main factors: a steady increase in the proportion of patients with gliomas in the overall structure of oncological morbidity, and the lack of breakthrough achievements in treatment outcomes for patients with this pathology, despite partial successes in fundamental and clinical oncology, the expansion of the arsenal of antitumor chemotherapy, and improvements in the technical equipment of diagnostic and neurosurgical departments [38].

Among all neoplasms of the central nervous system, gliomas occupy a leading position, accounting, according to various estimates, for 40–45% of all intracranial tumors [1, 18, 23, 37]. Approximately 70% of primary brain tumors are represented by various gliomas, more than half of which already have a high degree of malignancy at the time of diagnosis (high-grade gliomas; WHO grade III–IV according to the World Health Organization (WHO) classification) [29]. Conditionally benign gliomas (low-grade gliomas; WHO grade I–II according to the WHO classification) are relatively rare: in the United States, no more than 1,500 patients are registered annually [32]. Overall, the global incidence of various types of gliomas is estimated at 10–13 cases per 100,000 population [8, 30, 31]. At the same time, at least 10,000 newly diagnosed cases of primary neuroepithelial brain tumors are registered annually in the Russian Federation, and this figure demonstrates a steady upward trend [16].

The main reasons for this increase are conventionally divided into two groups: absolute and relative. Absolute factors include all determinants that directly contribute to an actual rise in the number of newly occurring neoplasms, such as the rapid aging of the population in economically developed countries, the gradual accumulation of hazardous mutations within the human population, which increase the potential risk of tumor development, deterioration of the environmental situation, and high rates of urbanization, along with the associated changes in lifestyle and dietary habits.

A relative factor, paradoxically, is the widespread implementation of population-based screening programs and the development of high-technology medical care, which facilitate more frequent and earlier detection of tumors. Despite the fact that the incidence of gliomas is observed across all age groups, these tumors most commonly occur in patients aged 30–60 years [11, 17, 33], i.e., they affect the most economically active segment of the population. Compared with women, men have a 1.5:1 higher risk of developing gliomas, and the risk in the elderly compared with younger individuals is 3.2:1.

The prerequisites for studying the pathogenesis of glial brain neoplasms and for developing methods for their diagnosis and treatment were advances in general surgery (the introduction of ether anesthesia and the principles of asepsis and antisepsis) and in the physiology of the central nervous system (the development of functional mapping of brain regions), which laid the foundation for the emergence of neurosurgery as an independent discipline [10, 31]. The first successful operations for the removal of intracranial tumors were performed by British surgeons William MacEwen in 1879 and Alexander Hughes Bennett in 1884. These works served as a starting point for further research in this field. However, despite the more than century-long history of neuro-oncology and the use of modern scientific advances in the treatment of gliomas, over the past 30 years the average life expectancy of such patients has increased by only a few months [17, 34].

The clinical classification of glial neoplasms, which ensures uniformity of treatment strategy and accuracy of prognosis, is based on the principles of tumor localization, histogenesis, and the activity of the neoplastic process.The localization principle предполагаes the division of tumors into groups depending on their site of origin (according to the name of the cerebral lobe/lobes or

individual brain structures) and their spread within the brain parenchyma. According to epidemiological studies, the approximate frequency of glioma involvement in different regions of the brain in adult patients is as follows [14, 24]:• **Cerebral hemispheres** — 70% (including: frontal lobe — up to 19%, temporal lobe — up to 13%, parietal lobe — up to 9%, occipital lobe — up to 2%, combined involvement of multiple lobes — approximately 28%);

- **Corpus callosum** — 5%;
- **Subcortical ganglia** — 6%;
- **Cerebral ventricles** — 7%;
- **Optic nerves and chiasm** — 1–1.5%;
- **Brainstem** — 6%;
- **Cerebellum** — 4–4.5%.

Depending on the histogenetic origin of the tumor clone's precursor cell, a pathomorphological classification of gliomas has been developed, which distinguishes the following categories [42]:

1. Astrocytic tumors
2. Oligodendroglial tumors
3. Oligoastrocytic tumors
4. Ependymal tumors
5. Tumors of the choroid plexus
6. Other neuroepithelial tumors
7. Neuronal and mixed neuronal–glial tumors
8. Pineal gland tumors
9. Embryonal tumors

In contrast to classifications of glial neoplasms based on anatomical localization—primarily intended to optimize surgical strategy—the pathomorphological classification is of fundamental importance for therapeutic decision-making. It plays a key role in the selection of chemotherapeutic regimens, determination of prognosis, stratification of patients in clinical trials, and advancement of basic and translational research in neuro-oncology.

In the vast majority of cases, gliomas are represented by tumors arising from astrocytic lineage cells and, less frequently, from oligodendrocytes. Neoplasms such as ependymomas, choroid plexus papillomas, neuroblastomas, pinealomas, and others, although essentially neuroectodermal tumors, are usually not considered within the category of gliomas, as they differ significantly from gliomas in their biological and clinical characteristics [17]. The classification of glial tumors developed by the World Health Organization (WHO) according to the activity of the tumor process, i.e., the degree of malignancy, distinguishes four grades. Grade IV represents the most active, rapidly growing, poorly differentiated or undifferentiated malignant tumors (e.g., glioblastoma, pineoblastoma), whereas Grade I includes a group of gliomas characterized by slow, minimally invasive growth and a high degree of differentiation of tumor cells (e.g., pleomorphic xanthoastrocytoma, myxopapillary ependymoma) [42].

A decisive role in determining the degree of activity (malignancy) is played by histological examination of the tumor specimen obtained during surgical removal or stereotactic biopsy. The assessment criteria are based on the presence of nuclear atypia, the number of pathological mitoses, endothelial proliferative activity, the severity of necrotic changes, and a number of other histological features. In some cases, especially when analyzing material from almost undifferentiated tumors, immunohistochemical studies or genotyping of the neoplasm are recommended to уточify the diagnosis (assessment of telomerase activity, high expression of

GFAP, VEGF, IGF-1 and their receptors, epithelial membrane antigen, Ki-67, and other markers of malignant tumors of the central nervous system) [10, 36].

A characteristic feature of glial tumors of the brain is invasive growth, in which there is macroscopically no clear boundary between the tumor and normal brain tissue; the brain parenchyma is usually infiltrated by tumor cells at a considerable distance from the primary tumor focus. This type of tumor growth is most typical of rapidly growing high-grade gliomas such as anaplastic astrocytomas and glioblastomas and is associated with an unfavorable prognosis. As with most malignant tumors, anaplastic types of gliomas are characterized by intensive development of a pathological vascular network, which accelerates tumor growth, increases the rate of invasion and metastasis, and also raises the risk for patients due to the possibility of hemorrhage into the tumor and adjacent tissues [22]. The nodular type of growth with a more or less clearly defined boundary and minimal infiltration is observed significantly less frequently and is most commonly seen in relatively benign gliomas (WHO grade I–II), which are associated with a more favorable treatment prognosis.

The clinical manifestations of glial tumors of the brain include a wide variety of general cerebral and focal organic symptoms of varying severity, depending on the location and volume of the neoplasm, as well as syndromes of intracranial hypertension, hydrocephalus (in cases of cerebrospinal fluid pathway obstruction), and, in advanced stages, dislocation syndrome. Pathognomonic symptoms are generally absent. In the early stages of tumor development, the disease may manifest with isolated signs (dizziness, epileptic seizures, sensory disturbances, etc.), which often makes it impossible to establish either a topographic diagnosis or to determine the hyperplastic nature of the pathological process. In some cases, the diagnosis of a brain tumor is an incidental finding on computed tomography or magnetic resonance imaging performed by a neurologist during the evaluation of a patient with various complaints. Currently, magnetic resonance imaging of the brain is considered the “gold standard” for the diagnosis of brain tumors. In certain cases, additional valuable information may be provided by magnetic resonance angiography, magnetic resonance spectroscopy [40], functional magnetic resonance imaging, single-photon emission computed tomography, multislice computed tomography, multislice computed tomographic angiography, and positron emission tomography [20]. The complexity of treating malignant gliomas requires a comprehensive approach and the involvement of a wide range of specialists. The first among them is the neurosurgeon. The main objectives addressed during surgical intervention are maximal reduction of the tumor volume and obtaining tissue for histological examination. At the same time, one of the key conditions of surgery is the preservation of functionally active brain areas in order to prevent clinically significant neurological deficits and to maintain the highest possible quality of life for the patient.

The infiltrative growth pattern of the tumor, the absence of clear boundaries of the tumor mass, and the proximity of functionally significant brain structures sharply limit (and in practice almost exclude) the possibility of radical surgical removal of gliomas. Nevertheless, striving for this goal is necessary: the extent of tumor resection positively correlates with overall survival, the time to tumor progression, and the need for repeat surgical intervention [39, 41].

The high invasive activity and metastatic potential of gliomas have been most clearly demonstrated in a number of clinical studies [28, 34, 35], which revealed an unusual increase in the frequency of distant tumor growth foci when treatment outcomes of the primary tumor site improved (maximal cytoreduction, aggressive radiotherapy, and chemotherapy). In our view, this assumption is not entirely correct, as it establishes a direct cause-and-effect relationship between these two events. Most likely, in cases where tumor growth appeared at a distance from the surgical site after some time, a multifocal glioma with a distant focus (metastasis) undetected prior to surgery was present. Adequate treatment slowed the rate of tumor progression in the primary zone, and the growth of the metastatic lesion in a distant brain region became clinically apparent.

A significant reduction in the volume of a malignant glioma may, in some cases, prevent the development of intracranial hypertension syndrome and obstruction of cerebrospinal fluid pathways, as well as reduce the severity of neurological symptoms by eliminating direct compression of adjacent brain structures by the tumor mass and by the gradual reduction of perifocal edema, ultimately improving the patient's quality of life. It should be noted that the correlation between the extent of tumor resection and overall survival may be less pronounced in cases where the glioma responds well to subsequent radiotherapy and chemotherapy [14].Thus, one of the main objectives of glioma surgery is to increase the radicality of tumor resection. This can be achieved through the development of methods that allow more precise intraoperative verification of tumor boundaries, as well as techniques aimed at improving intraoperative destruction of residual tumor tissue within the surgical field.

The former includes the use of various neuronavigation systems that make it possible to preoperatively plan the optimal surgical approach and course of the operation, taking into account functional brain mapping (functional magnetic resonance imaging with identification of motor and speech areas, magnetic resonance tractography, etc.), to navigate during surgery, and to visualize on a monitor the position of surgical instruments relative to the tumor and surrounding brain structures by correlating preoperative magnetic resonance images with the intraoperative view. Certain limitations inherent to neuronavigation systems, such as errors caused by changes in the topography of brain structures due to compression by the tumor mass or mechanical brain shift during surgery, can be compensated for by the use of intraoperative magnetic resonance or computed tomography neuroimaging.

When operating in functionally eloquent areas of the brain, intraoperative electrophysiological monitoring techniques are employed, including intraoperative evoked potentials and other methods that help prevent damage to functionally active regions and the development of postoperative neurological deficits [7, 12].

In addition to radiological imaging modalities used for intraoperative navigation and assessment of the extent of tumor resection, ultrasound scanners may also be applied. However, in this case, the complexity of data interpretation should be taken into account, which is associated with the heterogeneity of tumor tissue itself, its echogenic characteristics, the conditions of intraoperative scanning, transducer properties, and other factors.

The use of operating microscopes is currently the standard in neurosurgical procedures. To improve the accuracy of distinguishing residual tumor tissue from normal brain tissue, various intraoperative metabolic navigation techniques have been proposed, such as fluorescent labeling of tumor tissue using a fluorophore (5-aminolevulinic acid) [5, 6]. This requires additional equipment of the operating microscope with a fluorescence module or the use of a laser spectral analyzer. However, different types of gliomas do not accumulate the fluorophore to the same extent, which significantly limits the applicability of this method and increases the likelihood of diagnostic errors [5, 39]. A promising method for perioperative elimination of residual tumor tissue is intraoperative radiation therapy (IORT), which allows for targeted destruction of unresected fragments of glioma. For this purpose, the use of a low-energy X-ray source is optimal, such as the INTRABEAM PRS 500 system (Carl Zeiss) or its analogues, which are already widely applied in neuro-oncology. The system is mobile and safe; irradiation is performed in a standard operating room, the procedure takes a short time, and it is generally well tolerated by patients. Although a high ionization density is created in the tumor tissue and the surrounding tumor bed, the radiation effect on deeper structures is minimal, and the risk of systemic side effects is practically absent.

Among the wide range of methods for intraoperative tumor destruction used during "open" surgery, the use of cryoablation remains a matter of discussion. This method has several advantages, such as the ability to achieve, with a high probability, a sufficient zone of cell death at a certain distance from the cryoprobe, minimal risk of complications, absence of cumulative effects, and no significant obstacles to subsequent radiotherapy or chemotherapy.

During open surgery, the cryodestructor is applied to treat the tumor bed, stop bleeding from damaged vessels, and is also used as a holding instrument [3].Complete cryo-treatment of the tumor bed involves performing multiple destructions of the bed in cases of doubt about the radicality of tumor removal. However, even in this case, the function of these areas is irreversibly impaired, and the zones of cryonecrosis turn into cerebral debris, not to mention that tumor cells may be more resistant to low temperatures than differentiated brain tissue cells. The hemostatic effect of the cryodestructor also cannot be considered reliable, as it consists of the formation of an "ice thrombus" in the vessel, and therefore, after "thawing," bleeding may resume, especially in the presence of hemostatic disorders, which usually accompany surgical operations. When using a cryodestructor for fragmenting and removing a tumor, it is important to remember that the size of the tissue hypothermia zone around the ice sphere is relatively small (a few millimeters), and exceeding its limits will result in ordinary bleeding from small vessels. Consequently, if this condition is not met, the hemostatic effect of cryoexcision of gliomas is reduced. In addition, the cryodestructor is a complex device that requires preparation for operation, the allocation of an additional staff member for its maintenance, and has certain inconveniences when working in the depth of the wound.

With the development of neuroimaging methods, patients with small-volume tumors without significant "mass effect," deep localization, or tumors located near functionally significant areas, and therefore difficult to access for removal, are increasingly being identified. The generally accepted tactic in this case is stereotactic tumor biopsy, followed by deciding on the use of chemoradiotherapy in various options. For this procedure, both frame-based and frameless stereotactic systems (e.g., BRW [Brown-Roberts-Wells] system, CRW [Cosman-Roberts-Wells] system, Leksell system, etc.) are widely used, employing modern algorithms for stereotactic calculations [2, 15, 25]. Moreover, stereotactic biopsy, as the method of choice, is applied in patients with various contraindications to surgery (e.g., chronic heart failure of a high functional class, decompensated diabetes mellitus, etc.), including contraindications to general anesthesia, as well as in cases when different neuroimaging methods have not provided a conclusive answer regarding the etiology of a brain mass [27].

For relatively small gliomas, a promising approach may be a technique combining biopsy with stereotactic cryodestruction. After obtaining a tumor fragment for examination, the entire volume of the glioma is frozen by sequential insertion of the cryoprobe into planned coordinate points. In this case, the zones of cryodestruction must overlap, covering the entire volume of the tumor and the perifocal zone, which is achievable using a computerized planning system in the preoperative stage [13, 26]. At present, the number of patients in whom a brain tumor is diagnosed for the first time at a stage when the tumor volume significantly exceeds the possible freezing zone has increased. In such cases, stereotactic cryodestruction is suggested by some authors as a palliative intervention, as one of the stages aimed at improving the patient's condition prior to radical surgery or slowing tumor growth, thereby increasing the patient's life expectancy [13, 25].

At the same time, the volume of such a procedure should be sufficiently large, since single cryodestructions within the tumor mass do not reduce its volume and do not bring significant benefit, due to the minimal reduction in the total number of highly proliferative cells, which does not lead to a noticeable decrease in the overall tumor growth rate. Conversely, excessive cryonecrosis of tumor tissue, potentially involving the peritumoral area, can contribute to the development of perifocal edema, disrupt compensatory mechanisms, and lead to displacement syndrome [9].

The use of brachytherapy methods through stereotactic implantation of radioactive sources, such as iridium-192 (192Ir), iodine-125 (125I), or palladium-103 (103Pd), has not yet gained widespread use, primarily due to the complexity of handling radioactive activity and the high frequency of complications. However, research in this promising area continues.

Currently, the main component of the treatment complex for most patients with gliomas remains conventional radiotherapy. According to the current standard, 2–4 weeks after surgery,

irradiation of the tumor bed and a two-centimeter peritumoral zone is performed, with a total focal dose of 55–60 Gy, usually at 2 Gy per fraction (25–30 fractions per course), from multiple fields in a stationary mode or rotation, over 5–6 weeks. Critical elements for increasing the effectiveness of radiotherapy include the dose distribution pattern, the high likelihood of radiation damage to the skin and functionally significant brain areas, and the systemic effects of ionizing radiation on the patient's body (immunosuppression, anemia, hypercoagulable syndromes, etc.), which significantly limit the possibility of repeated courses of radiotherapy. A significant problem is also the development of radiation necrosis in the long-term post-treatment period (up to 15% of cases), which requires differential diagnosis from recurrent tumors. Continuous improvements in the hardware and planning systems of radiotherapy provide hope for improved outcomes of this treatment method in the near future [19].

Another highly effective innovative method of external beam radiotherapy is radiosurgery, or stereotactic radiosurgery, which allows delivering the full radiation dose precisely to the tumor focus in a single procedure, with minimal impact on surrounding tissues. In theory, this enables complete destruction of the tumor nodule, provided its size does not exceed 3 centimeters in diameter. This method is implemented using fixed radiation sources such as Cobalt-60 (GammaKnife) and mobile linear accelerator systems (CyberKnife). For tumors larger than 3 centimeters, CyberKnife allows for hypofractionated external beam radiotherapy with the formation of a complex-shaped irradiation field—stereotactic radiotherapy.

In the context of radiotherapy development, studies on the use of proton therapy and boron neutron capture therapy for the treatment of glial tumors appear promising. However, these treatment methods are still at the stage of development and clinical trials.

The possibilities of antitumor chemotherapy at the present stage are limited to prolonging the recurrence-free period, extending patient survival, and improving quality of life. Drugs are used according to approved treatment standards, depending on the histological structure of the tumor, either as monotherapy or in specific combinations.

Chemotherapy is always associated with a high risk of side effects, such as hematotoxicity, and the development of cardiac, hepatic, and/or renal insufficiency, which significantly limits the options for effective tumor treatment regimens and requires appropriate supportive therapy [21, 22]. The main directions of research aimed at improving the effectiveness of chemotherapy include the development of new drugs, optimization of the administration regimens of already used agents, and the application of targeted approaches, including individualized selection of chemotherapy regimens based on the tumor cells' sensitivity to major groups of cytostatics, among others [4].

Conclusion. Gliomas remain one of the most challenging problems in modern neuro-oncology due to their high prevalence, aggressive biological behavior, infiltrative growth, and limited long-term treatment outcomes. Despite significant advances in neuroimaging, microsurgical techniques, radiotherapy, and chemotherapy, radical tumor eradication is rarely achievable, and overall survival has improved only modestly. Effective management of gliomas requires a multidisciplinary and individualized approach that integrates maximal safe surgical resection, precise histopathological and molecular diagnosis, and rational use of adjuvant therapies. Further progress in understanding glioma pathogenesis and in developing targeted and intraoperative treatment technologies is essential for improving prognosis and quality of life in affected patients.

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