CLINIC, DIAGNOSIS AND TREATMENT OF GLIAL TUMORS OF THE FRONTAL LOBES OF THE CEREBRAL HEMISPHERES

Sabirov Jasurbek Oltiboyevich

Master student in Medicine. Department of Neurosurgery.
Republican Specialized Scientific and Practical Medical Center for Neurosurgery, TASHKENT

Abstract: *Despite significant achievements in oncology and neurosurgery, glial brain tumors continue to be an urgent problem of modern health care. The specific gravity of gliomas in the general structure of glial neoplasms is 40-45%, mainly they are detected at the age of 30-60 years, affecting the most able-bodied part of the population. Glial neoplasms, as a rule, develop from cells of the astrocytic or oligodendrocyte population and are characterized by rapid growth rates of the primary tumor node, invasiveness, predilection for early metastasis, high frequency of recurrence and unfavorable prognosis. The article presents a modern clinical classification of gliomas, based on the principles of localization, histogenesis and activity of the tumor process. A characteristic feature of glial brain tumors is invasive growth with the absence of a macroscopically distinct boundary between the tumor and normal brain tissue. This type of growth is typical for fast-growing high-grade gliomas (anaplastic astrocytomas, glioblastomas), it is characterized by an unfavorable prognosis. As with most malignant tumors, anaplastic types of gliomas are characterized by intensive development of the pathological vasculature, which accelerates the growth rate of the neoplasm, the rate of invasion and metastasis, and also increases the risk for patients due to the possibility of hemorrhage into the tumor. Nodal type of growth with a clearly delineated border and insignificant infiltration is less common, with conditionally benign gliomas that have a more favorable prognosis for treatment. The article gives a detailed review of the main surgical, radiological and chemotherapeutic directions of treatment with gliomas. Finally, it is concluded that the described methods do not exhaust all suggestions for increasing the effectiveness of treatment of glial tumors and the development of new methods will bring neurooncologists closer to solving this topical problem.*

Keywords: *brain tumors; glioma; glioblastoma; neuroimaging; chemotherapy.*

КЛИНИКА, ДИАГНОСТИКА И ЛЕЧЕНИЕ ГЛИАЛЬНЫХ ОПУХОЛЕЙ ЛОЮНОЙ ДОЛИ БОЛЬШИХ ПОЛУШАРИЙ ГОЛОВНОГО МОЗГА.

Сабиров Ж.О.[1]

[1]Сабиров Жасурбек Олтибоевич - магистр 3-курса. Кафедра нейрохирургии.
Республиканский специализированный научно-практический медицинский центр нейрохирургии, г.Ташкент

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на значительные достижения в области онкологии и нейрохирургии, глиальные опухоли головного мозга продолжают оставаться актуальной проблемой современного здравоохранения. Удельный вес глиом в общей структуре глиальных новообразований составляет 40-45%, в основном они обнаруживаются в возрасте 30-60 лет, что влияет на наиболее трудоспособную часть населения. Глиальные новообразования, как правило, развиваются из клеток популяции астроцитов или олигодендроцитов и характеризуются быстрыми темпами роста первичного опухолевого узла, инвазивностью, склонностью к раннему метастазированию, высокой частотой рецидивов и неблагоприятным прогнозом. В статье представлена современная клиническая классификация глиом, основанная на принципах локализации, гистогенеза и активности опухолевого процесса. Характерной особенностью опухолей глиальных головного мозга является инвазивный рост с отсутствием макроскопически отличной границы между опухолью и нормальной мозговой тканью. Этот тип роста характерен для быстрорастущих полноценных глиом (анапластических астроцитомах, глиобластомы), он характеризуется неблагоприятным прогнозом. Как и в случае большинства злокачественных опухолей, анапластические типы глиом характеризуются интенсивным развитием патологической сосудистой сети, которая ускоряет темпы роста новообразования, скорость инвазии и метастазов, а также увеличивает риск для пациентов из-за возможности кровоизлияния в опухоль. Узловой тип роста с четко очерченной границей и незначительной инфильтрацией реже встречается с условно доброкачественными глиомами, которые имеют более благоприятный прогноз для лечения. В статье дается подробный обзор основных хирургических, радиологических и химиотерапевтических направлений лечения глиомами. Наконец, делается вывод о том, что описанные методы не исчерпывают всех предложений по повышению эффективности лечения глиальных опухолей, и разработка новых методов приблизит нейроконтологов к решению этой актуальной проблемы.

Ключевые слова: *опухоли головного мозга; глиомы; глиобластома; нейровизуализации; химиотерапия.*

Gliomas (neuroectodermal, neuroepithelial tumors) are primary tumors of the central nervous system originating from glia cells that make up the parenchyma of the brain. Interest in the problem of glial brain tumors is currently caused by two main factors: a steady increase in the proportion of patients with gliomas in the overall structure of oncological morbidity and the absence of breakthrough achievements in the treatment outcomes of patients with this pathology, despite the private successes of fundamental and clinical oncology, the expansion of the arsenal of antitumor chemotherapy and increasing the technical equipment of diagnostic and neurosurgical departments

[1]. Among all neoplasms of the central nervous system, gliomas occupy a leading place, accounting for, by various estimates, 40-45% of all intracranial tumors [2]. About 70% of primary brain tumors are represented by various gliomas, of which more than half at the time of diagnosis already have a high degree of malignancy (high grade gliomas; WHO grade III-IV grade according to the classification of the World Health Organization (WHO)) [3]. Conditionally benign gliomas (low grade gliomas, WHO grade I-II degrees according to WHO classification) are relatively rare: in the US, no more than 1500 patients are registered annually [4].

In general, the incidence of various types of gliomas in the world is 10-13 cases per 100 thousand population [5]. At the same time, only in the Russian Federation, at least 10,000 new cases of primary neuroepithelial brain tumors are registered annually and this indicator has a steady tendency to increase [6]. The main reasons for this growth are conventionally divided into two groups: absolute and relative. Absolute factors include all factors directly contributing to the increase in the incidence of neoplasms, such as the rapid aging of the population of economically developed countries, the gradual accumulation in the human population of dangerous mutations that increase the potential risk of tumor development, environmental degradation and high rates of urbanization, closely related changes way of life and the nature of people's nutrition.

The relative circumstance is, paradoxically, the widespread introduction of clinical examination and the development of high-tech methods of medical care that promote more frequent and early detection of tumors. Despite the fact that the incidence of gliomas is characteristic for all age groups, as a rule, these tumors are found in patients aged 30-60 years [7], ie, the most able-bodied part of the population is affected. In comparison with women, the risk of developing gliomas is 1.5: 1 in men, and 3.2: 1 in elderly people compared to young ones. The prerequisites for studying the pathogenesis of glial neoplasms of the brain, the development of methods for their diagnosis and treatment were the achievements of general surgery narcosis, aseptic and antiseptic rules) and the physiology of the central nervous system (the development of functional mapping of the brain regions), which initiated the development of neurosurgery as an independent discipline [8]. The first successful surgery for the removal of intracranial tumors was carried out 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 a century-long history of neuro-oncology and the use of modern science for the treatment of gliomas, the average life expectancy of such patients has increased by only a few months in the last 30 years [9].

The clinical classification of glial neoplasms, which ensures the unity of treatment tactics and the accuracy of the prognosis, is based on the principles of localization, histogenesis and activity of

the tumor process. The localization principle assumes the division of tumors into groups depending on the place of their origin (by the name of the proportion / fraction of the brain or individual brain structures) and the spread in the brain substance. According to epidemiological studies, the frequency of lesions of gliomas of different parts of the brain in adult patients is approximately [10]:

- cerebral hemispheres - 70% (including: frontal lobe - up to 19%, temporal - up to 13%, parietal - up to 9%, occipital - up to 2%, combination of lesions of different lobes - about 28%);
- corpus callosum - 5%;
- subcortical ganglia - 6%;
- Ventricles of the brain - 7%;
- optic nerves and chiasma - 1-1,5%;
- brain stem - 6%;
- cerebellum - 4-4,5%.

Depending on the initial histological type of the precursor cell of the tumor clone, a pathomorphological classification of gliomas has been created, which involves the allocation of several categories [11]:

1) astrocytic tumors;
2) oligodendroglial tumors;
3) Oligoastrophic tumors;
4) ependymary tumors;
5) tumors of the choroid plexus;
6) other neuroepithelial tumors;
7) neuronal and mixed neuronal-glial tumors;
8) tumors of the pineal gland;
9) embryonic tumors.

In contrast to the classification of glial neoplasms based on their localization and intended mainly to optimize the tactics of surgical treatment, pathomorphological classification is of paramount importance for the selection of chemotherapy, determining the prognosis for the development of the disease, and for basic research in neurooncology. In the overwhelming majority of cases, gliomas are represented by tumors developing from cells of the astrocytic series, less often, from oligodendrocytes. Such neoplasms as ependymomas, choroid papillomas, neuroblastomas, pinealomas and others, referring in essence to neuroectodermal neoplasms, are nevertheless not considered within the framework of gliomas, since they differ significantly from the latter in their biological and clinical features [12]. The classification of glial tumors by the World Health Organization based on the activity of the tumor process, that is, the degree of malignancy, implies the isolation of four degrees, where the IV degree is the most active, fast-growing, low-grade or undifferentiated, malignant tumors (eg, glioblastoma, pineoblastoma), and I degree - a group of gliomas, characterized by slow, minimally invasive growth and a high degree of differentiation of tumor cells (for example, pleomorphic xantoa strozitoma, myxopapillary ependymoma) [13].

A decisive role in determining the degree of activity (malignancy) is played by methods of histological examination of the tumor preparation obtained by its removal or stereotactic biopsy. Evaluation criteria are based on the presence of nuclear atypism, the number of pathological mitoses, the proliferative activity of the vascular endothelium, the severity of necrotic changes, and a number of other

histological criteria. In some cases, especially when analyzing material from virtually undifferentiated tumors, immunohistochemistry or genotyping of the neoplasm (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) [14].

A characteristic feature of glial brain tumors is invasive growth, in which there is no macroscopic clear boundary between the tumor and normal brain tissue, the cerebral parenchyma, as a rule, is infiltrated by tumor cells at a considerable distance from the primary neoplasm node. This type of tumor growth is most typical for fast-growing high-grade gliomas such as anaplastic astrocytomas, glioblastomas and is characterized by an unfavorable prognosis. As for most malignant tumors, anaplastic types of gliomas are characterized by intensive development pathological vascular network, which accelerates the growth rate of neoplasm, the rate of invasion and metastasis, and also increases the risk to patients due to the possibility of hemorrhage into the tumor and adjacent tissue [15]. Nodal type of growth with a more or less clearly delineated border and insignificant infiltration is much less common, most often with conditionally benign gliomas (grade I-II according to the classification of the World Health Organization) that have a more favorable prognosis for treatment. Clinical manifestations of glial brain tumors are represented by a variety of cerebral and focal organic symptoms of varying severity in accordance with the localization and volume of neoplasm, intracranial hypertension syndromes, hydrocephalus (in the occlusion of cerebrospinal fluidways) and, in far-reaching cases, dislocation syndrome. Pathognomonic symptoms, as a rule, are absent. In the early stages of development, the tumor can manifest by single signs (dizziness, epileptic seizures, sensitivity disorders, etc.), which often does not allow us to establish a topical diagnosis or determine the hyperplastic nature of the pathological process. In a number of cases, the diagnosis of a brain tumor is an accidental finding on a computer or magnetic resonance imaging when a patient is examined by a neurologist in connection with one or another of the complaints. Currently, magnetic resonance imaging of the brain is the "gold standard" of diagnosing brain tumors. In some cases, magnetic resonance angiography, magnetic resonance spectroscopy [16], functional magnetic resonance imaging, single-photon emission computed tomography, multispiral computed tomography, multispiral computed tomography angiography, positron emission computer tomography [17] can provide the necessary additional information. . The complexity of treatment with malignant gliomas requires an integrated approach and the involvement of a number of specialists. The first in this series is a neurosurgeon. The main tasks that are solved in the course of surgical intervention are the maximum reduction in the volume of neoplasm and the obtaining of material for histological examination.

At the same time, one of the conditions for surgical intervention is the preservation of functionally active brain areas to prevent a clinically significant neurological deficit and the maximum possible preservation of the patient's quality of life. The infiltrative nature of tumor growth, the absence of distinct boundaries of the tumor node and the proximity of functionally significant brain structures severely limit (virtually exclude) the possibility of radical surgical removal of gliomas. Nevertheless, it is necessary to strive for this: the volume of tumor removal positively correlates with life expectancy, with the time of the appearance of continued growth of the neoplasm and the need for repeated intervention [18].

High invasive activity and metastatic potential of gliomas are most vividly demonstrated in a number of clinical studies [19], which revealed an unusual increase in the incidence of distant foci of neoplasm growth with improved treatment results for the primary tumor site (maximally complete cytoreduction, aggressive radiation and chemotherapy). In our opinion, this assumption is not entirely correct, since it conducts a direct causal relationship between these two events. Probably, in those cases, when, at some time after the operation, tumor node growth occurred at a distance from the intervention site, there was a multifocal glioma with a distant focus (metastasis) not detected before the operation. Adequate treatment slowed the rate of continued growth in the initial zone and the growth of tumor metastasis in the distant region of the brain came to the forefront. A significant decrease in the volume of malignant glioma allows in a number of cases to prevent the development of the syndrome of intracranial hypertension and the occlusion of the cerebrospinal fluidways, to reduce the severity of neurological symptoms by eliminating the direct compression of the nearby brain structures by the tumor node and the gradual reduction of perifocal edema, which ultimately improves the patient's quality of life. It should be noted that the correlation of tumor removal volume and life expectancy may not be so clearly expressed in the case of glioma response to radiation and chemotherapy in the future [20].

Thus, one of the main tasks of gliomas surgery is to increase the radicality of tumor removal. This is solved by developing methods that allow more accurate verification of the boundaries of neoplasm during surgical intervention, and ways to improve intraoperative destruction of tumor tissue in the surgical intervention area.

The first can include the use of various neuronavigation systems that allow you to plan in advance the optimal access and the course of the operation, taking into account the mapping of functional brain areas (functional magnetic resonance imaging with identification of motor and speech zones, magnetic resonance tractography, etc.), orientate during surgery and To see on the monitor the position of the surgical instrument in relation to the tumor and the surrounding brain structures, comparing the preoperative magnetic resonance images with the Tina

surgical field. Certain shortcomings inherent in neuronavigation systems, for example, errors caused by changes in the topography of brain structures when they are compressed by the volume of tumor tissue or by mechanical displacement during surgery, can be compensated by the use of intraoperative magnetic resonance imaging or computer tomographic neuroimaging.

When working in the field of functionally active areas of the brain, intraoperative electrophysiological control techniques are used, including intraoperative evoked potentials and a number of other techniques that prevent damage to the functionally active zones and the occurrence of postoperative neurologic deficits [21]. In addition to radiotherapy for the purposes of intraoperative navigation, quality control of tumor removal, ultrasound scanners are also possible, but in this case, the complexity of the interpretation of the obtained data must be taken into account, due to the heterogeneity of the tumor tissue itself and its echogenic characteristics, conditions of location in the operating field, other factors. The use of operating microscopes is now the standard for surgical interventions on the brain. To improve the accuracy of recognition of tumor remnants and brain tissue, various methods of intraoperative metabolic navigation are suggested, for example, "staining" the tumor tissue with fluorophore (5-aminolevulinic acid) [22]. This requires additional configuration of the microscope with a fluorescent module, or the use of a laser spectro-analyzer. However, different gliomas do not accumulate a fluorophore to an equal degree, which significantly limits the possibilities of using this method and increases the probability of errors [23].

A promising method of perioperative elimination of tumor tissue remains is intraoperative radiation therapy (IORT), which allows to accurately destroy unfortunate fragments of glioma. For this task, it is optimal to use a source of low-energy X-ray radiation, for example, the INTRABEAM PRS 500 system (Carl Zeiss) or its analogs, which are already widely used in neurooncology. The system is mobile and safe, the irradiation is carried out under the conditions of a normal operating room, the procedure takes a short time, is satisfactorily tolerated by patients. Despite the fact that a high density of ionization is created in the tumor tissue and tissues of the tumor bed, the radiation effect on the more deeply located structures is minimal, the risk of developing systemic side effects is practically absent.

Of the wide range of methods for intraoperative destruction of tumors used during the "open" operation, the issue of using cryodestruction remains controversial. This method has a number of positive properties, such as the possibility of a high probability of obtaining a sufficient zone of death of all cellular elements at a certain distance from the cryoprobe, a minimal risk of complications, no cumulation of the effect and significant obstacles to the further use of radiation and chemotherapy.

During an open operation, the cryodestructor is used to treat the tumor bed, stop bleeding from damaged vessels, and

is also used as a restraining tool [23]. Complete cryoprotection of the tumor bed implies the fulfillment of multiple destruction of the bed when doubting the radicality of neoplasm removal. However, the function of these sites is still irreversibly broken, and the cryoconecrosis zones turn into cerebral detritus, not to mention the fact that tumor cells may be more resistant to low temperatures than differentiated cells of brain tissues. The haemostatic effect of the cryodestructor can also not be considered reliable, since it consists in the formation of an "ice thrombus" in the vessel, and therefore, after "thawing", bleeding can resume, especially with the development of hemostasis disorders, usually accompanying surgical operations.

When using a cryodestructor for fragmentation and removal of the tumor, it must be remembered that the magnitude of the tissue hypothermia zone around the ice sphere is relatively small (a few millimeters) and going beyond it will lead to ordinary bleeding from small vessels. Consequently, if this condition is not met, then the haemostatic effect of cryoextirpation by gliomas is reduced. In addition, the cryodestructor is a complex device that requires preparation for work, the allocation of an additional employee for its maintenance, and also has certain inconveniences when working in the depth of the wound. With the development of methods of neuroimaging, patients with tumors of small volume without significant "mass effect", deep localization or located near functionally significant zones are increasingly being detected, and therefore difficult to remove. A common tactic in this case is a stereotactic biopsy of the tumor with the subsequent decision of the question of conducting chemoradiotherapy in various variants. Frame and frameless stereotactic systems (for example, BRW system, brown-Roberts-Wells system, CRW system (Cosman-Roberts-Wells), Leksell, etc.) are widely used for this procedure, using modern algorithms of stereotaxic calculations [24]. In addition, stereotactic biopsy, as a method of choice, is used in patients with various contraindications to surgery (chronic heart failure of high functional class, decompensated diabetes mellitus, etc.), including contraindications to general anesthesia, and in cases when various methods of neuroimaging did not provide an exhaustive answer about the etiology of brain volume formation [25].

With relatively small amounts of gliomas, a technique that combines biopsy with stereotactic cryodestruction may be promising. After taking a fragment of the tumor, the study will freeze the entire volume of glioma by sequentially introducing a cryoprobe into the planned coordinate points. The cryodestruction zones must overlap each other, capture the entire volume of the tumor and the perifocal zone, which is possible with the use of a computerized planning system at the preoperative stage [13].

At present, the number of patients in whom the neoplasm of the brain is diagnosed for the first time at a stage where the tumor volume considerably exceeds the size of the possible freezing zone has increased. In this case, stereotactic cryo-

destruction is proposed by several authors as a palliative intervention, as one of the stages in order to improve a patient's condition before a radical operation or to slow the growth of a tumor, which increases the life expectancy of the patient [21].

At the same time, the volume of such an operation should be quite large, since single cryodestruction in the tumor thickness does not reduce its volume and does not bring significant benefit, due to a slight decrease in the total number of cells with high proliferative activity, which does not lead to a noticeable gain in the decrease growth rate of the tumor as a whole. Conversely, excessive cryonecrosis of tumor tissue, with possible involvement of the peritumoral region, may contribute to the growth of perifocal edema, lead to the disruption of compensatory mechanisms and the development of a dislocation syndrome [9].

The use of brachytherapy methods by stereotactic implantation of radioactive sources, for example, iridium-192 (192Ir), iodine-125 (125I), palladium-103 (103Pd), has not yet become widespread, primarily due to the complexity of working with activity and high the frequency of complications, but research in this promising area continues. Currently, the main element in the treatment complex of most patients with gliomas remains conventional radiation therapy. According to the current standard, after 2-4 weeks after the operation, irradiation of the bed of the removed tumor and two centimeters of the perifocal zone with a total focal dose of 55-60 Gy, usually 2 Gy per fraction (25-30 fractions per course), from several fields in a stationary mode or in rotation, for 5-6 weeks. Critical elements for increasing the effectiveness of radiation therapy are the nature of dose distribution, the high probability of radiation damage to the skin and functionally significant brain areas, and the systemic effect of ionizing radiation on the patient's body (immunosuppression, anemic, hypercoagulable syndromes, etc.), which significantly limits the possibility of repeated courses radiotherapy. An important problem is also the formation of radiation necrosis in the long-term treatment period (up to 15% of cases), requiring differential diagnosis with a recurrent tumor.

Continuous improvement of the hardware and radiotherapy planning systems allows us to hope for an improvement in the results of this method of treatment in the near future [19]. Another highly effective innovative method of remote radiation therapy is radiosurgery or stereotactic radiosurgery, which allows one to precipitately apply a full dose of radiation to a tumor focus in a single procedure with minimal impact on surrounding tissues. In theory, this allows complete destruction of the tumor node, provided that its dimensions do not exceed 3 centimeters in diameter. This technique is implemented on the installation using fixed sources of radiation 60 Co (GammaKnife) and installations with mobile linear accelerators (CyberKnife). With a tumor size of more than 3 centimeters on CyberKnife, large-fractionated remote radiation therapy with the formation of an

irradiation field of a complex shape is also possible - stereotactic radiotherapy. As part of the development of radiation therapy, studies on the use of captive therapy in the treatment of glial tumors with proton therapy are promising, but these methods of treatment are still at the stage of development and clinical studies. The possibilities of antitumor chemotherapy are limited at the present stage and consist in increasing the duration of the disease-free period, prolonging the life of patients and improving its quality. The drugs are used in accordance with approved treatment standards, depending on the histological structure of the tumor, both in monotherapy mode and in a specific combination.

Conducting chemotherapy is always associated with a high risk of side effects, such as hematotoxicity, cardiac, hepatic and / or renal insufficiency, which significantly limit the choice of effective regimens for the tumor and require the appropriate accompanying therapy [21, 22]. The main research areas for the purpose of increasing the effectiveness of chemotherapy are the creation of new medicines, the optimization of prescribing patterns of already used drugs, the use of targeted techniques, including individual selection of chemotherapy regimens based on the sensitivity of tumor cells to the main groups of cytostatics, etc. [4]. In conclusion, it should be noted that the above methods do not exhaust all suggestions for increasing the effectiveness of treatment of glial tumors and, perhaps, in the future, the development of new methods will bring neurooncologists closer to solving this topical problem.

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