Diagnosing Brain Tumors with Magnetic Resonance Imaging (MRI)

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ABSTRACT

Cerebral glial tumors remain a significant issue in contemporary medicine, despite considerable breakthroughs in oncology and neurosurgery. Cerebral gliomas make up approximately 40-45% of all glial tumors. These tumors are typically diagnosed in individuals aged 30-60, affecting the most able-bodied segment of the population. Glial tumors typically originate from astrocytic or oligodendrocytes cell populations and are characterized by a high growth rate, invasiveness, early metastatic ability, high rate of recurrence and an unfavourable prognosis. Invasive growth with no distinct macroscopic border between the tumor and normal brain tissue is a characteristic feature of glial brain tumors. This type of growth is typical of fast-growing, highly malignant gliomas such as anaplastic astrocytomas and glioblastomas. An unfavorable outcome is typical of anaplastic gliomas. These malignant tumors are known for their intensive development of a pathologic vascular network, which accelerates tumor growth and increases the risk of metastasis and cerebral hemorrhage within the tumor. Nodal growth types with distinct borders and moderate infiltration are less typical and may be found in cases of conditionally benign gliomas with a more favourable prognosis.

The aim of the study. To study the features of blood flow using MR perfusion in planning and monitoring radiation therapy for brain gliomas to predict the likelihood of recurrence.

Conclusion. Highly informative methods of radiation research can be used to image the brain, estimate the size, shape, and structure of neoplasms, determine their position in the brain, identify the presence and prevalence of edema, and assess the areas and degree of brain tissue damage

Keywords: cerebral tumors; brain tumors; neurooncology; neurosurgery, neurovisualization. aniqlash, miya to'qimalarining shikastlanish joylari va darajasini aniqlashga imkon beradi

Introduction. Gliomas are primary tumors of the central nervous system that initially arise from glial cells that make up the brain parenchyma. The worldwide incidence of various types of gliomas is 1013 cases per 100,000 population [8, 22, 25]. The interest in glial brain tumors is currently driven by the increasing number of glioma patients in the general structure of oncological morbidity and the lack of significant progress in treating this pathology, despite the successes of fundamental and clinical oncology, expansion of the arsenal of antitumor chemotherapy, and increasing technical equipment of diagnostic and

neurosurgical departments [5]. Gliomas are the most common type of central nervous system neoplasm, accounting for approximately 40-45% of all intracranial tumors [1, 18, 26]. To ensure consistent treatment and accurate prognosis, clinical classification of glial neoplasms is based on tumor localization, histogenesis, and activity. The principle of localization involves categorising tumors into groups based on their origin within specific brain structures and their spread throughout the brain. Epidemiologic studies tentatively report that gliomas affect different parts of the brain (GM) in adult patients as follows: hemispheres of the large brain - 70% (including frontal lobe - up to 19%, temporal lobe - up to 13%, parietal lobe - up to 9%, occipital lobe - up to 2%, combination of lesions of different lobes - about 28%); corpus callosum - 5%; subcortical ganglia - 6%; brain ventricles - 7%; optic nerves and chiasma - 1-1. 5%; brainstem - 6%; cerebellum - 4-4.5%. Gliomas are a type of tumor that can affect individuals of all ages, but are more commonly found in patients between the ages of 30 and 60. Men are at a higher risk of developing gliomas than women, with a ratio of 1.5:1. Additionally, the elderly are at a higher risk compared to the young, with a ratio of 3.2:1 [11, 17, 21, 26]. A pathomorphological classification of gliomas has been created based on the initial histological type of the precursor cell of the tumor clone. This classification involves several categories, including astrocytic tumors, oligodendroglial tumors, oligoastrocytic tumors, ependymal tumors, chorioid plexus tumors, other neuroepithelial tumors, neuronal and mixed neuronal-glial tumors, pineal gland tumors, and embryonal tumors. Unlike the classification of glial neoplasms based on their localization, which is mainly intended to optimize surgical treatment tactics, the pathomorphological classification is of primary importance for selecting chemotherapy, determining the prognosis of the disease, and conducting basic research in neuro-oncology. Approximately 70% of primary brain tumors are gliomas, with over half being highly malignant (G grade III-IV according to the WHO classification) at the time of diagnosis. The degree of malignancy is determined by histologic examination methods.

According to the World Health Organization (WHO), glial tumors are classified based on the activity of the tumor process, specifically the degree of malignancy. This classification system involves four degrees, with the fourth degree being the most active and consisting of fast-growing, low-differentiated or undifferentiated, malignant tumors (e.g.,...). The text describes different types of gliomas, including grade II and III gliomas, which are characterized by rapid growth and invasion, and grade I gliomas, which grow slowly and have a high degree of tumor cell differentiation. The evaluation criteria are based on various histologic criteria, such as the presence of nuclear atypism, the number of pathologic mitoses, proliferative activity of vascular endothelium, and severity of necrotic changes.

In some cases, especially when analyzing material from practically undifferentiated tumors, immunohistochemical study or genotyping of the neoplasm (study of telomerase activity, high expression of GFAP, VEGF, IGF-1 and receptors to them, epithelial membrane antigen, Ki-67 and other markers of malignant tumors of the central nervous system) is recommended to clarify the diagnosis [10]. [10]. A characteristic feature of glial brain tumors is invasive growth, in which macroscopically there is no clear boundary between the tumor and normal brain tissue, the brain parenchyma is usually infiltrated with tumor cells at a considerable distance from the primary node of the neoplasm. This type of tumor growth is most typical for rapidly growing highly malignant gliomas such as anaplastic astrocytomas, glioblastomas and is characterized by an unfavorable prognosis. As for the majority of malignant tumors, anaplastic types of gliomas are characterized by intensive development of pathological vascular network, which accelerates the growth rate of the neoplasm, invasion and metastasis rates, and also increases the risk for patients due to the possibility of hemorrhage into the tumor and adjacent tissues [23]. Nodular type of growth with more or less clearly delineated border and insignificant infiltration occurs much less

frequently, most often in conditionally benign gliomas (I-II degree according to WHO classification), which have a more favorable prognosis of treatment. Clinical manifestations of glial brain tumors are represented by a variety of general cerebral and focal organic symptoms of varying severity according to the localization and volume of the neoplasm, syndromes of intracranial hypertension, hydrocephalus (in case of occlusion of liquor passages) and, in advanced cases, dislocation syndrome.

Pathognomonic symptoms are usually absent. At early stages of development, the tumor may manifest with single signs (dizziness, epileptic seizures, sensory disturbances, etc.), which often does not allow to establish either a topical diagnosis or to determine the hyperplastic nature of the pathological process. In a number of cases, the diagnosis of brain tumor is an incidental finding on CT or MRI when the patient is examined by a neurologist in connection with certain complaints. High invasive activity and metastatic potential of gliomas have been most clearly demonstrated in a number of clinical studies [24], which revealed an unusual increase in the incidence of distant foci of neoplasm growth with improved treatment results of the primary tumor node area (maximal complete cytoreduction, aggressive radiation and chemotherapy). Magnetic resonance angiography, magnetic resonance spectroscopy, functional magnetic resonance imaging, single photon emission computed tomography, multispiral computed tomography, multispiral computed tomography angiography, positron emission computed tomography can provide the necessary additional information in complex diagnostics [20,22,25]. For a long time computed tomography (CT) remained the only method of diagnostics of intramedullary volumetric brain masses, and detection of glial brain tumors according to CT data is performed by indirect signs, which, first of all, include structural disorders: deformation, tissue displacement, edema.

MSCT method allows convincingly distinguishing neuroepithelial tumors among volumetric intramedullary brain formations. X-ray contrast preparations provide additional information about the structure and features of the pathological focus, relationships with surrounding tissues, character of vascularization. The use of contrast agents in the diagnosis and localization of gliomas is of great importance in case of diffuse growth of the formation [3]. However, according to a number of authors, some voluminous glial masses with diffuse growth do not accumulate contrast agent or accumulate it in insufficient quantity for visualization [18,19,24]. Currently, the "gold standard" for diagnosing brain tumors is magnetic resonance imaging of the brain. The advantages of MRI include its high resolution, possibility of tissue contrasting, multiparametric scanning. The use of MRI under contrast enhancement (CE) conditions has proved to be the most effective [3]. The use of MRI with CG allows differentiating tumors from non-tumor lesions of the GM, clarifying the structure, localization and volume of neoplasms, their relationship with surrounding tissues, the state of the blood-brain barrier (BBB). MR-perfusion has great opportunities in differential diagnostics and evaluation of treatment efficiency of malignant brain tumors. In addition, further evaluation and follow-up of patients who have undergone primary line of therapy pose a separate problem.

Patients with brain tumors are recommended to undergo regular dynamic MR imaging examinations to detect early signs of disease progression, allowing further treatment tactics to be determined as soon as possible. However, routine MRI often fails to confidently distinguish early stages of tumor progression from treatment-related changes, including necrosis and pseudoprogression. The urgency of the problem of reliable detection of continued growth of malignant glial tumors (GBT) is due to the need to determine the tactics and start treatment at an early stage [5-8]. The analysis of the literature shows that to date there is no unified point of view and a generally accepted algorithm of examination to solve this problem due to a wide range of diagnostic methods, each of which has its advantages and disadvantages [21,29]. Pathophysiologically, the essence of the problem lies in the damage of HEB by ionizing

radiation, as a result of which the destroyed vascular endothelium causes the phenomenon of increased tissue contrasting, which in some cases is practically indistinguishable from the manifestations of ABM at MRI [9]. Besides, it is known that the use of new cytotoxic drugs and angiogenesis blockers, although allowing to increase the life expectancy of patients with cerebral tumors, but such methods of treatment are indiscriminate. As a result, in addition to the therapeutic effect directly on the tumor itself, there are adverse toxic reactions to adjacent brain regions, which can mimic tumor progression [10]. Directly at the physiologic level, the term perfusion refers to the level of blood delivery to a tissue element, measured by capillary blood flow. The magnitude of perfusion depends on blood volume and blood flow velocity. There are contrast-free and contrast-dependent MR perfusion studies, each with its own advantages and disadvantages. The advantages of contrast-free perfusion include non-invasiveness and safety of its performance. The method of spin labeling of arterial blood was proposed by S. Takano et al. in 1992. In their work devoted to the study of rat brain perfusion, they showed the possibility of using water contained in arterial blood as an endogenous contrast agent [27]. A brief characterization of the technique consists in the inversion of spins of hydrogen atoms under the action of radiofrequency pulses of MR tomograph. After 1.5-2.0 s, labeled protons of arterial blood enter the brain, where they replace protons of intercellular fluid, resulting in a slight decrease in the magnetization of water, which makes it possible to estimate the cerebral blood flow. Despite the technically complicated organization of obtaining reliable results of MR-perfusion, technological improvement of equipment and software provided further possibility of perfusion application in routine clinical practice. In general, this technique is similar to the principle of isotope studies using labeled atoms and molecules, but perfusion does not require the use of radioactive agents, which provides an advantage for repeated studies, neurological or vascular tests [12]. Such advantages of contrast-free MR perfusion open wide prospects for its clinical application for the diagnosis of tumors, cerebral circulatory disorders, vascular malformations, epilepsy, degenerative diseases, as well as basic scientific research on the study of developmental and aging processes [13]. A significant aspect in the study of cerebral perfusion when performing MRI is the use of exogenous extracellular magnetic resonance contrast agent, using either the ability of gadolinium-containing contrast agent to influence the T2*-echo signal (visualization of MR perfusion weighted by magnetic susceptibility with dynamic contrast enhancement at the first pass), in another case assessing the change of T1signal from time after administration of gadolinium-containing contrast agent [14]. Magnetic susceptibility-weighted MR visualization with dynamic contrast enhancement, known in foreign literature as magnetic susceptibility-weighted perfusion with dynamic contrast enhancement, is a technique in which the passage of a bolus of contrast agent through the brain is monitored using a series of 115 T2or T2-weighted images. The susceptibility effect of the paramagnetic contrast agent results in a decrease in signal on the signal intensity-time curve. The information on the received signal can be converted into a time-dependent curve of paramagnetic substance concentration for each pixel. The obtained data serve as a basis for the construction of parametric maps of cerebral blood flow volume and cerebral blood flow velocity. MRI CU T2-perfusion in the examination of the brain allows visualization and quantitative assessment in a short period of study, being the most common and reliable method of diagnostics of brain tumors. Disadvantages of this technology may include difficulties in determining absolute values of cerebral blood flow volume, sensitivity to artifacts (such as blood elements, calcification, metal, air, and bone), possible problems in visualizing the skull base, and operator dependence. Dynamic contrast-enhanced MR perfusion, also known as "permeability" MRI, consists of acquiring a series of T1-weighted images before, during, and after administration of extracellular low molecular weight gadoliniumcontaining drugs. Subsequent

construction of a time-dependent signal intensity curve reflects perfusion parameters such as vascular permeability and extravascular volume. Dynamic contrast enhancement in MR imaging of perfusion is used to determine the kinetic parameters of accumulation, plateau, and washout of contrast agent from tissue, which provides information about tissue properties at the microvascular level. The equations describing concentration changes during the passage of a bolus of a pharmacologic drug in dynamic MRI, the so-called concentration-time curve, were first used in 1990. [15]. The shape of this curve for artery and vein displays arterial and venous functions, which are used to describe hemodynamic tissue parameters. The main ones are the volume of cerebral blood flow measured by the area under the curve, the time to reach the peak concentration corresponding to the center of gravity or peaks on the graph, and the transit time of the contrast agent determined by the width of the curve. The result of such a study is the construction of perfusion maps for each index for ease of perception performed in different shades of the color scale. This allows to visually determine the zone of interest and with the help of further calculations to obtain quantitative values of the listed parameters, on the basis of which a graphic curve is constructed [16,17]. Compared to MR perfusion with dynamic contrast enhancement allows to study in detail quantitative indices of GEB and microvascular system permeability and gives a more complete assessment of brain tumor angiogenesis. The disadvantages of DCU MRI technology include the complexity of image acquisition, the need to build a pharmacokinetic model, and the lack of widespread and relatively easy-to-use software for postprocessing processing of results. Tumor progression and response to treatment are associated with a complex interaction between proliferative changes in vasculogenesis and infiltration of viable tumor cells, as well as multiple therapeutic effects, including endothelial cell death, vascular thrombosis, and hemorrhage. Many authors agree that these processes, arising from disruption of the GEB and increased edema, are difficult to distinguish on standard MRI [18-20]. But these processes differ markedly in their metabolic activity and blood supply requirements. Neovascularization is an early stage of tumor growth, blends with the natural vasculature, facilitating hyperperfusion of normal brain [21,23]. This state of vascular proliferation contrasts sharply with the opposite state, ischemic, which is found in areas exposed to ionizing radiation. To characterize such changes, the term "radiation injury" is used, which has several temporal correspondences. Thus, the occurrence of acute radiation reactions can be talked about directly during radiation exposure to the body or immediately after its completion [26,28]. Early delayed radiation injuries occur during the first 4 months, late ones - later than this period. According to different data [29], depending on the fractionation mode, individual sensitivity of the patient and some other factors, the incidence of radiation damage is 3-24%. Radiation damage is characterized by the presence of: radiation leukoencephalopathy; focal lesions including either contrast-positive foci in the white matter or a more severe form - radiation necrosis; secondary radioinduced tumors [19]. The difficulty of differential diagnosis is due to the fact that on routine MR tomograms the most frequently encountered focal radial lesions have extremely similar PRO characteristics. The similar nature of contrast enhancement and the effect of volume exposure also cause the development of perifocal edema [20,23]. In addition, the complexity is that BMD can be observed at any time and coincide with one or another stage of radiation damage development. All this requires the use of additional methods of radial diagnostics to differentiate these two conditions [3,10,17,18,19]. The study of MR-perfusion capabilities for differentiation of radiation damage and PRO 48 states is found in many domestic and foreign studies. The authors analyzed the data of 33 patients with brain tumors after combined treatment who underwent routine MR-study supplemented by perfusion technique with bolus contrasting. As a result, perfusion-weighted imaging with contrast enhancement made it possible to distinguish between areas of increased

(corresponding to PRO) and decreased (corresponding to radiation damage) cerebral blood flow, which was a defining differential criterion [15]. The ability to detect morphological vascularization of tissue and to distinguish it from avascular necrosis allowed us to conclude that MR perfusion technique is highly effective in differential diagnosis of glial tumor recurrence and radiation necrosis [19,20,21]. V. Vuorinen [28] notes high accuracy of differentiation of tumor tissue and areas of radiation damage using MR-perfusion was noted. However, the authors indicated that due to the considerable variability in the optimal reported thresholds, more research is required to standardize them and to develop a specific quantitative perfusionweighted imaging strategy that is consistent between treatment facilities. Early analysis of MR tomograms in patients during and after chemoradiation treatment has revealed many difficulties in correctly interpreting the findings due to the presence of areas of necrotic transformation, residual tumor tissue, parenchymatous gliosis, and "inactive" neoplasm [7,9,11]. Although increased perfusion is usually associated with the process of neoangiogenesis in the tumor [17,19], some authors believe that it may also indicate the appearance of hypervascularized areas - regeneration of microcirculatory vessels, which reduces the severity of hypoxic phenomena and improves drug delivery to tumors [21,24,27]. The study of R. Mangla et al. [20] showed that the perfusion status of postoperative cavity walls on MRI after chemoradiation treatment can be a significant predictor of the time of progression in patients with malignant brain tumors. The researchers hypothesized that MR perfusion data may serve as a prognostic biomarker for subsequent chemotherapy and identify individuals who are more likely to respond to its use. An area with increased perfusion possibly indicates increased delivery of chemotherapy, whereas decreased perfusion impedes delivery of therapeutic agents, severely reducing the efficacy of chemotherapy. This view has been supported by recent clinical trials reporting that combination therapy that provides vascular regeneration is associated with favorable outcome in tumor lesions of the head and neck as well as in metastatic colorectal, renal, and lung cancer [21]. Another known problem in evaluating the results of therapy of malignant gliomas, which requires additional examination, is pseudoprogression, which is observed in 20-30% of patients who received chemoradiation therapy. The appearance and enlargement of areas of pathologic contrast enhancement in the marginal zone of the postoperative defect after combined treatment are visually noted during 3 months of follow-up [16,18]. The interval of the first 12 weeks after completion of radiation therapy is also recommended by the leading neuro-oncology working group RANO, which also studied this issue [14]. The phenomenon of pseudoprogression is caused by radiation-induced endothelial damage, vascular dilatation and fibrinoid necrosis, and inflammatory changes of the GEB. Although its pathophysiology is still unclear, chemical exposure is thought to induce a transient local inflammatory response, edema, and increased vascular permeability, which is manifested by increased signal on postcontrast images [21,23]. Accurate differentiation between pseudoprogression and continued growth is crucial to make informed treatment decisions. When perfusion imaging was used, true progression showed a higher maximum CBV than pseudoprogression, which was confirmed by radiologic and clinical data in several studies (sensitivity and specificity 81.5 and 77.8%, respectively) [27]. A promising direction of studying MR-perfusion technique is its use as predictors of survival after completion of chemoradiation treatment [24,25]. A number of studies have shown that the increase in maximal cerebral blood flow using such an index as normalized blood flow between initial and follow-up images was a better prognostic factor for a shorter progression-free period ($p=0.01$) than the increase in tumor diameter ($p=0.049$) [24,27]. At one-month post-radiation therapy, R. Mangla et al. [22] found that increased nBV was predictive of poor one-year overall survival (sensitivity 90% and specificity 69%), while tumor size did not provide this information. Nevertheless, the results of the mentioned works were mixed, as another study showed

that perfusion imaging was inferior in predicting survival, whereas tumor size determined by T1- and T2-weighted imaging had prognostic value [23]. Some authors [26,28] have shown that 25% of patients with recurrent glioblastomas treated with sediranib exhibit increased perfusion, and these patients had higher progression-free and overall survival than patients with stable or decreased perfusion. This was confirmed in patients with newly diagnosed glioblastomas whose treatment consisted of radiation therapy, temozolomide, and sediranib. Patients with increased perfusion had longer median overall survival than patients with decreased perfusion (overall survival 504 days vs. 321 days). In particular, the problem of differential diagnosis of gliomas according to the degree of malignancy by means of MRI with KU remains unsolved [4]. Such a direction of radiation diagnostics as magnetic resonance spectroscopy (MRS), which allows quantitative assessment of a number of biochemical parameters characterizing volumetric formations and the state of GM tissues, continues to develop [3,29]. With the development of MRS, an additional possibility of metabolic studies with determination of the level of some tissue metabolites, such as choline, N-acetylaspartate, creatinine, etc., appeared. According to some authors, choline concentration is the main indicator that should be relied on in the diagnosis of tumors. Increased choline levels are characteristic of gliomas of II and III degrees of malignancy and, on the contrary, in gliomas of IV degree of malignancy may decrease [5,6]. According to the literature, the sensitivity, specificity, and diagnostic accuracy of the 1H-MRS method in the differential diagnosis of brain tumors range from 79-100, 74-86, and 83-86%, respectively [22,25,27]. The authors state that the concentration of choline in the tumor increases with the degree of malignancy of gliomas, but in the presence of necrosis in glioblastomas, the level of choline may be low [6]. Differential diagnosis of neoplasms is difficult when residual tumor tissue is located in the area of radiation necrosis or vasogenic edema [25]. Despite the great opportunities, a number of diagnostic and differential-diagnostic tasks in the use of MRI remain unsolved. First of all, it concerns the problems of assessing the state of metabolism of neoplasms, the degree of their malignancy, vascularization, hypoxicity, as well as the possibility of early assessment of tumor response to treatment. The experience of using contrast-enhanced MRI has shown that the level of contrast agent accumulation in tumor tissue depends on a number of parameters, such as the state of neoplasm microcirculation, the degree of HEB disruption, the volume of intercellular space in the tumor and therefore does not always accurately reflect the nature of the lesion [7]. Treatment tactics in radiation necrosis and in continued growth of neoplasms differ radically. At the same time, the presence of altered or damaged tissues in the investigated postoperative zone, detected at MRI with KU, can serve as a source of false-positive diagnostics in the identification of continued tumor growth [8]. In this case, the contrast agent enters the intercellular space due to the emerging GEB disturbances, which is not associated with the presence of viable tumor cells in the studied area. Thus, the accumulation of contrast agent in the lesion area during MRI can simulate continued tumor growth, which complicates data interpretation. It has been shown that the specificity of MRI with contrast in detecting recurrent gliomas does not exceed 70% [9]. Assessment of the response of neoplasms to treatment by CT or MRI methods is usually based on the detection of changes in the size and structure of neoplasms. However, changes in the size and structure of pathologic neoplasms, even in case of successful treatment, can be detected after many months and can not always serve as a reliable criterion for evaluating the effectiveness of treatment. A direct dependence of growth and progression of malignant glioma tumors on the degree of their vascularization has been revealed, which became the basis for searching for ways to block the process of neovasculogenesis in order to affect brain tumors resistant to cytotoxic drugs [10]. There is great interest in the use of technologies that allow to assess hemodynamics, and the key importance is attached to the determination of blood flow and

oxygen transport in tumor tissue [11]. For this purpose, perfusion magnetic resonance imaging can be successfully applied. At present, radiation imaging methods such as routine MRI, MR spectroscopy, diffusion-weighted MRI, MR tractography, functional MRI, and others have taken a firm place in the diagnostic algorithm for detecting glioma tumors. A great deal of experience has been accumulated that allows differentiating tumors, determining their localization, position, shape, structure, and size. However, the questions of biological and histochemical properties of the detected volumetric formations, metabolic disorders in the adjacent parts of GM tissues, as a rule, cause difficulties or remain beyond the limits of these methods. The problem of differentiation of radiation necrosis from continued tumor growth in postoperative areas has not been solved, which complicates early assessment of the effect of treatment.

Conclusion Adequate treatment slows down the rate of continued growth in the original area, and the growth of tumor metastasis in the distant area of the brain came to the forefront. A significant reduction in the volume of malignant glioma allows in some cases to prevent the development of intracranial hypertension syndrome and occlusion of liquor pathways, to reduce the severity of neurological symptomatology due to the elimination of direct compression of nearby brain structures by the tumor node and gradual reduction of perifocal edema, which eventually improves the patient's quality of life. It should be noted that the correlation between tumor removal volume and life expectancy may not be so clearly expressed in case of glioma response to further radiation and chemotherapy [14,27]. Thus, one of the main tasks of glioma surgery is to increase the radicality of tumor removal. This is solved by the development of radiation methods, including multiparametric MRI with the combination of CG. The use of MRI allows solving the most difficult differential-diagnostic problems and brings fundamentally new additional data to the summary view of the investigated formation. However, if for MRI the consistent development of the method capabilities has been carried out universally for several decades, the capabilities of multiparametric MRI and its combination with CG need to be further explored.

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