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MODERN IMAGING TECHNIQUES IN THE ASSESSMENT OF MALIGNANCY IN GLIAL BRAIN TUMORS: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Gliomas represent a major group of primary central nervous system tumors, accounting for approximately 80% of all malignant brain neoplasms. Recent advances in molecular diagnostics, including the identification of mutations in the isocitrate dehydrogenase (IDH) gene, offer new opportunities to improve the classification of gliomas and to understand the mechanisms of their development. IDH mutations, which are found in a large proportion of gliomas, are associated with a better prognosis and represent an important biomarker for the development of targeted therapeutic strategies. Diagnostic techniques, particularly magnetic resonance imaging (MRI), also play an important role, providing additional ways to assess the morphological and biological characteristics of gliomas, contributing to a more accurate determination of tumor malignancy and molecular profile, which is key to treatment decisions.*

The purpose was to study the po*ssibilities of magnetic resonance imaging in assessing the degree of malignancy of glial brain tumors.*

Method: *A literature review was performed using the keywords: glioma, IDH mutation, IDH wild-type, MRI, magnetic resonance spectroscopy (MRS), apparent diffusion coefficient (ADC), diffusion-weighted imaging (DWI), diffusion tensor imaging (DTI), diffusion kurtosis image (DKI), Susceptibility Weighted Imaging (SWI) in PubMed, BMC Medicine, and Google Scholar databases. The review includes the results of an analysis of 45 literature reviews on the diagnostic capabilities of molecular diagnostics and MRI to assess the malignancy of gliomas.*

Results: *This review highlights the importance of current approaches to the diagnosis of gliomas, demonstrating that different grades of malignancy and IDH mutation status are associated with unique features on MR imaging, including differences in localization, signal, and enhancement patterns. DTI and DWI extend the ability of MRI to assess tissue microstructure, allowing for more precise tumor characterization. Studies combining MRI morphologic features, ADC and DTI parameters offer a non-invasive approach to glioma prognosis, highlighting the importance of integrated use of imaging modalities to improve diagnosis and therapy.*

Conclusion: *The use of magnetic resonance imaging allows for more accurate morphologic and metabolic characterization of gliomas in assessing the degree of malignancy, allowing physicians to make more accurate prognostic assessments and select the most appropriate treatment strategy.*

Keywords: *Glioma, IDH mutation, wild-type IDH, MRI, magnetic resonance spectroscopy, ADC, DWI, DTI, DKI, SWI.*

Introduction: Gliomas are the main group of primary CNS tumors [1]. Gliomas are classified based on histopathological distribution into low-grade (LGG) and high-grade (HGG) gliomas. LGGs are generally well differentiated, while HGGs are characterized by low differentiation and the resulting worse prognosis [2]. However, recent studies emphasize the limitations of traditional histopathological classification that highlight the significant heterogenicity of gliomas. This complicates their accurate diagnosis using standards methods such as proliferation marker tests and cell morphology analyzes [3].

A significant reform of the 2007 World Health Organization (WHO) classification of CNS tumors introduced a grade I to IV gradation of gliomas depending on their histology, including such main types as astrocytomas, oligodendrogliomas, and ependymomas [4]. A revolutionary step was the introduction of molecular diagnostic results as an important diagnostic criterion for the classification of gliomas in 2016, which was further developed in subsequent 2021 guidelines that emphasize the value of molecular diagnostics in defining subgroups of glioma [4, 5]. This change confirms the importance of molecular diagnostics in the classification of CNS tumors, complementing traditional methods such as histology and immunohistochemistry.

Research since 2008 has highlighted the importance of isocitrate dehydrogenase (IDH) as an important molecular marker in oncology, especially with the discovery of IDH1 mutations in glioblastoma patients and, subsequently, IDH1 and IDH2 mutations in grade II and III gliomas. The presence of IDH mutations is associated with a more favorable prognosis compared to gliomas without these mutations, making them an important

element in determining clinical tactics and choosing a treatment method [6].

However, an exact preoperative differentiation between glioma grades and subtypes remains a challenging task due to the limited sensitivity and specificity of existing methods [7]. In this context, imaging techniques, especially magnetic resonance imaging (MRI), represent a valuable tool for the complementary diagnosis and molecular classification of gliomas, offering opportunities for a more accurate prediction of disease outcomes and treatment planning [8].

The purpose was to study the possibilities of magnetic resonance imaging in assessing the degree of malignancy of glial brain tumors.

Materials and Methods: This literature review includes articles and literature reviews on the capabilities of modern MRI techniques in neuroimaging. Data search was carried out on PubMed, BMC medicine, Google Scholar systems using keywords glioma, IDH mutation, wild type IDH, MRI, MRS, ADC, DWI, DTI, DKI, SWI in the database. A total of 116 publications were found, of which 45 sources were included in this review (Figure 1).

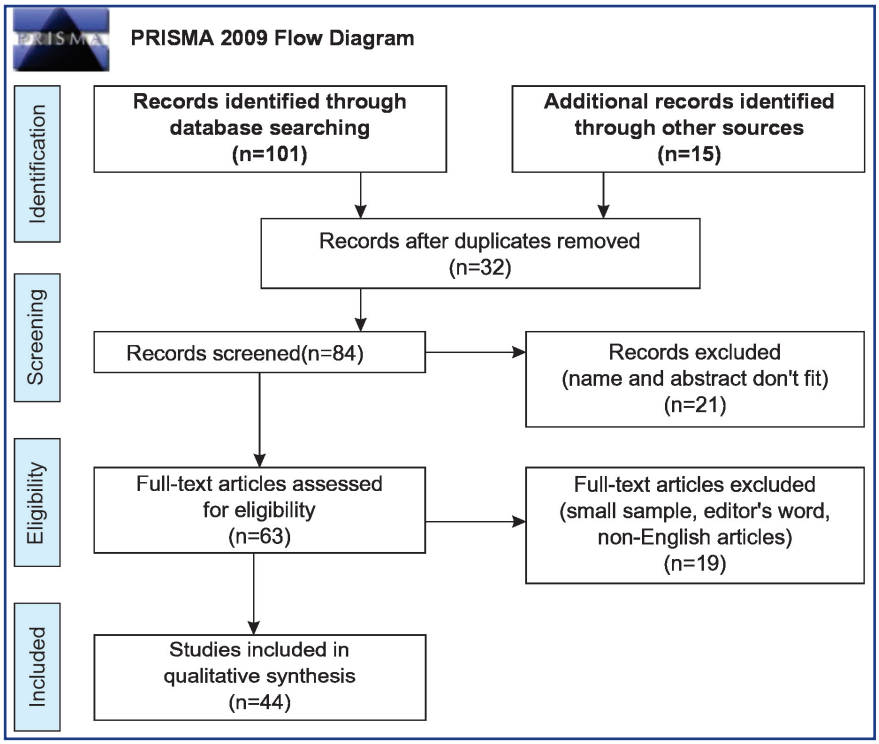

Figure 1 – Algorithm for selecting references

Results: MRI remains the method of choice for glioma visualization, providing detailed morphological characteristics and tumor enhancement data. The trials confirm that gliomas of varying grades and the status of the IDH mutation exhibit unique characteristics in the MR images, including differences in location, signal, and enhancement, which can serve as important diagnostic markers [9]. For example, some studies report the specificity of T2-FLAIR signal discrepancies for IDH-mutant astrocytomas of almost 100%. However, quantitative assessment of morphological characteristics remains a challenge to accurately predict the grade and molecular subtype of glioma [10].

Studies that combine MRI morphological characteristics and values with ADC to predict glioma grades and IDH mutation status emphasize the meaning of patient age for diagnostic purposes [11]. Wild-type IDH gliomas are more common in older patients; and age is associated with a worse prognosis in glioma. According to some authors, patients with HGG are on average older than those who suffer from LGG [12]. In particular, age over 60 was mentioned as an independent risk factor for predicting wild-type HGG and IDH gliomas, as age can be a key factor in determining treatment strategies [13].

Pathophysiological changes associated with disruption of the blood-brain barrier cause enhancement of contrast in glioma magnetic resonance images [14, 15]. The level of enhancement depends largely on the degree of barrier damage, so MRI enhancement features can indicate glioma malignancy [16]. In studies, most wild-type HGG and IDH gliomas exhibit ring enhancement, while gliomas with the LGG and IDH mutation are more likely to be hypovascular [11, 13, 17]. These differences in enhancement may serve as an additional criterion for differentiating between subtypes of glioma.

The tumor location and distribution influence the prognosis and treatment planning of patients with glioma. LGG more often affects one brain lobe, whereas HGG can spread to several lobes, including the mesolobus and insula [13]. In particular, IDH mutation gliomas

'prefer' certain locations, such as the frontal and temporal lobe and are less common in high-risk areas of the brain [18, 19]. Qi S. et al. analyzed the gene phenotype in 193 astrocytomas to reveal that IDH mutation gliomas were mostly localized in one lobe, such as the temporal lobe, frontal lobe or cerebellum. Wild-type IDH tumors were found in combined lobes such as the brain stem or diencephalon (p<0.001) [17]. Wang Y. et al. showed that tumor location in the frontal lobe was unilaterally highly correlated with IDH mutation gliomas (p<0.001) [18]. In the study by Gozé C. et al., 100% of LGG centered in the insula had IDH mutations [19].

DWI is an important MRI sequence that provides valuable information for the identification and differential diagnosis of various forms of cancer, including gliomas. This method is based on measuring the limitation of water diffusion in tissues, which increases with tumor cellularity. Calculating ADC from DWI provides a fast and efficient assessment that facilitates the classification of gliomas and even typing them based on the presence of an IDH mutation. However, the use of individual DWI parameters is often not sufficient to determine the grade of the tumor and the molecular subtype without additional context.

The studies by Du N. and Chen L. showed that the ADC value was inversely correlated with the number of tumor cells in gliomas. At that, the ADC values in high-grade gliomas were lower than in low-grade gliomas [12, 20]. This indicated damage to the structure of the white matter and limited diffusion of water in more aggressive tumors. In turn, wild-type IDH gliomas demonstrated lower ADC values compared to IDH mutation gliomas, highlighting differences in their cell density and structure [21]. Patel et al. noted that histologically observed microcysts tended to increase in LGGs with IDH mutation. This could explain higher ADC values in those cases, but this pathophysiological mechanism is understudied [22].

Multivariate logistic regression models including age, ADC parameters and qualitative MRI characteristics provide greater precision in distinguishing between LGG and HGG, and in identifying the status of IDH mutation [13]. Therefore, DWI is a powerful quantitative imaging tool that can noninvasively reflect the cellular structure by measuring the ADC diffusion coefficient. Edemas, necrosis, and hemorrhage in gliomas are closely associated with a poor prognosis [23]. The MRI morphological features of gliomas, including the grade of glioma and the status of IDH mutation, can significantly vary, influencing the prognostic assessment. HGGs are more often accompanied by cystic lesions and hemorrhaging, which may be due to the increased microvascular density and invasiveness of these tumors [13]. Du N. et al. revealed no significant differences between IDH-mutant and wild-type gliomas in terms of cystic lesion, hemorrhage, and peritumoral edema [13]. However, another study by Lasocki A. et al. demonstrated a statistically significant difference in the degree of edema between gliomas with and without IDH mutation. Therefore, the degree of edema in patients with IDH mutation was 5-33%, while most wild-type IDH patients had edema grade >33% (44% of wild-type IDH patients had edema grade 34-67%, and 14% had edema grade 68-95%) [24]. It should be noted that patients with wild-type IDH1 were more prone to bleeding compared to patients with the IDH1 mutation (15 vs 5; p=0.286) [25]. This may indicate biological differences between these groups of gliomas and their impact on clinical outcomes.

Studies emphasize that IDH mutations can influence the activation of hypoxia-inducible factor 1-alpha (HIF-1α), leading to suppression of angiogenesis [26]. Analysis of blood perfusion characteristics can contribute to the prognosis of gliomas with different mutation status of IDH. The use of dynamic-susceptibility contrast perfusion-weighted imaging (DSC-PWI) to measure relative blood volume (rCBV) provides important noninvasive information about microcirculation in tumors [27, 28].

In studies, rCBV in the brain varies significantly between IDH mutation gliomas and wild-type IDH gliomas. Xing Z. et al. revealed a much lower rCBV in gliomas with IDH mutation compared to wild-type IDH tumors [28]. Tumors without IDH mutations were associated with a higher rCBV [27]. This shows a significant potential for rCBV in evaluating the angiogenic activity of tumors with different IDH phenotypes, where higher values correlate with enhanced vascularization.

DTI improves DWI capacity. DTI can measure water diffusion in several directions, which is important for predicting the progression and recurrence of gliomas. The study of oligodendrogliomas by Xiong J. et al. showed that minimum ADC and maximum fractional anisotropy allow distinguishing gliomas by IDH status [29].

It is believed to be more accurate to reflect the complexity of water diffusion and tumor tissue heterogeneity than DTI. Therefore, DKI provides better results in detecting microstructural changes in gliomas of various grades and genotypes [30]. In the study of 58 cases of astrocytoma by Tan Y. et al., DKI parameters such as axial, radial, and medium kurtoses were significantly lower in IDH-mutated astrocytomas compared to wild-type tumors, demonstrating their usefulness in assessing the prognosis of the disease [31]. In similar studies of HGG and LGG by Zhao et al., the comparison revealed lower values of DKI parameters in LGG. This underlines the diagnostic value of these parameters, especially the axial kurtose, in determining IDH status with high sensitivity and specificity [32]. These parameters were also positively correlated with Ki-67 level, which confirms their importance in assessing tumor aggressiveness [33].

MRS denotes that 2-hydroxyglutarate (2-HG), a signature metabolite associated with IDH mutations, correlates with tumor cell proliferation. This method allows non-invasively determining the IDH mutation status and measuring the 2-HG level, which is impor-

tant for genotyping gliomas. Mutated IDH2 can produce more 2-hG than mutated IDH1 [34]. However, the complexity of in vivo spectral analysis can cause diagnostic difficulties [35]. Choi C. et al. reported that the reduction of the 2-HG level could evidence the treatment efficacy, especially with oligodendrogliomas [35]. In the study by Yano H. et al., the choline (Cho)/creatine (Cr) and Cho/ N-acetyl aspartate (NAA) ratios were significantly different between the mutated IDH and the wild-type IDH group. Reduced Cho/Cr or Cho/NAA ratios in the case of gliomas with unclear boundaries allows suggesting a wild-type IDH [36].

SWAN/SWI is an MRI method of high-res visualization of blood vessels and hemorrhages. SWI without contrasting can non-invasively indicate normal or intertumoral sensitivity signal intensity (ITSS) related to tumor grade. The study by Yang X. et al. revealed that ITSS values differed a lot between astrocytomas with IDH 2 + 3 and 4 grade mutations. This suggests a potential role of ITSS as a biomarker to classify IDH mutated astrocytic gliomas [37]. Similarly, Lin Y. et al. registered a significant difference in ITSS between the classes and proposed ITSS as a valuable biomarker for HGG accurate diagnostics [38].

Radiomics, an innovative area in medicine, focuses on prognosis and extracting medical knowledge by analyzing quantitative data from medical images. This approach provides a valuable additional clinical tool that is non-invasive and allows for a comprehensive assessment of the three-dimensional structure of the tumor, including its spatial heterogeneity. Although magnetic resonance imaging is traditionally used for primary diagnostics and post-treatment evaluation, radiomics expands the capacity of this technology to contribute to the preoperative classification and prediction of IDH mutational phenotypes [39]. Many radiomic models specifically consider the status of the IDH mutation in LGG and HGG [24, 40, 41]. Wild-type IDH gliomas demonstrate greater postcontrast enhancement compared to gliomas with the IDH mutation [24]. Further research, such as that of Liu X. et al., delved deeper into the analysis of these differences by looking at the quantitative characteristics of MRI images in 158 LGG and HGG cases with different IDH mutation status, where 14 imaging features were key to predict mutation status [42]. Despite recent achievements, the value of radiomics as a prognostic factor for patients with gliomas is still being studied. Research by Li Z. and Peeken J. highlights the potential of radiomics to improve the prognostic model of gliomas by integrating pathological, clinical and radiomic data [43, 44]. In the future, the further development of radiomics, increased data volumes, and better mathematical models will significantly improve the accuracy of diagnosis and individualized approach to the treatment of gliomas, contributing to a more accurate prediction of disease outcomes.

Discussion: This review highlights modern approaches to the diagnosis and classification of gliomas, focusing on the importance of molecular diagnostics and advanced imaging methods. Gliomas, which make up the majority of primary CNS tumors, represent a heterogeneous group of diseases with varying degrees of aggressiveness and prognosis. The traditional histopathological classification is recently updated with molecular research that significantly improves patient stratification and treatment planning [4].

The importance of molecular markers such as IDH mutations in predicting disease outcome and response to treatment is already well documented [6]. IDH mutations serve as an important prognostic factor and determine the new subgroup of gliomas with a relatively favorable outcome. Therefore, the integration of molecular diagnostics into clinical practice is a key step toward personalized medicine for patients with gliomas.

MRI plays a central role in the diagnosis of gliomas, providing valuable information about the size, shape, location, and relationship of the tumor to critical brain structures. The development of imaging techniques, including DWI and MRS, has expanded the capacity of MRI in assessing biological characteristics of tumors such as cell density and metabolic profile [45]. These methods can provide additional information to distinguish gliomas of various malignancies and determine their molecular status.

The application of radiomics to magnetic resonance data improves diagnostic accuracy and contributes to the development of prognostic models capable of predicting disease outcome based on non-invasive imaging [45].

Thus, the integration of molecular diagnostics and modern imaging techniques represents a promising approach to improve the treatment of patients with gliomas. This combination allows a more accurate tumor classification and provides important information for choosing the most appropriate treatment, considering the individual characteristics of the tumor and the patient. In the future, continued developments in molecular biology and medical imaging suggest a further improvement in glioma treatment strategies, including the emergence of new target therapies based on tumor-specific biomarkers.

Conclusion: MRI characteristics were related to glioma malignancy and IDH mutation status. Multivariate logistic regression models that combine MRI morphological characteristics with ADC parameters provide a non-invasive and preoperative approach to predicting glioma malignancy and IDH mutation status. MRI is widely used for preoperative evaluation and future monitoring of gliomas and provides information important for determining the degree of tumor malignancy. Glioma malignancy grade determines the choice of surgical treatment plan and prognosis for patients.

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АҢДАТПА

ГЛИАЛЬДЫ МИ ІСІКТЕРІНІҢ ҚАТЕРЛІ ІСІК ДӘРЕЖЕСІН БАҒАЛАУДАҒЫ ЗАМАНАУИ БЕЙНЕЛЕУ ӘДІСТЕРІ: ӘДЕБИЕТКЕ ШОЛУ

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Өзектілігі: *Глиомалар мидың барлық қатерлі ісіктерінің шамамен 80% алып жатқан орталық жүйке жүйесінің бастапқы ісіктерінің негізгі тобы болып табылады. Молекулярлық диагностикадағы заманауи жетістіктер, соның ішінде изоцитратдегидрогеназа (IDH) геніндегі мутацияларды анықтау глиомалардың жіктелуін жақсартуға және олардың даму механизмдерін түсінуге жаңа мүмкіндіктер ашады. Глиомалардың көп бөлігінде кездесетін IDH мутациялары анық болжаммен байланысты және мақсатты терапевтік стратегияларды әзірлеуге ықпал ететін маңызды биомаркер болып табылады. Сондай-ақ, диагностика әдістері, атап айтқанда МРТ маңызды рөл атқарады, олар глиомалардың морфологиялық және биологиялық сипаттамаларын бағалауға қосымша мүмкіндіктер береді, ісіктердің қатерлі ісік дәрежесін және олардың молекулалық профилін дәлірек анықтауға ықпал етеді, бұл емдеу туралы шешім қабылдауда маңызды.*

Зерттеудің мақсаты *– мидың глиальды ісіктерінің қатерлілік дәрежесін бағалауда магнитті-резонанстық томографияның мүмкіндіктерін зерттеу.*

Әдістері: *PubMed, BMC Medicine және Google Scholar мәліметтер базасында глиома, IDH мутациясы, IDH жабайы түрі, МРТ, магниттік резонансты спектроскопиясы (MRS), аппараттық диффузия коэффициенті (ADC), диффузиялық өлшенген бейнелеу (DWI), диффузиялық тензорлық бейнелеу (DTI), диффузиялық куртозды бейнелеу (DKI), магниттік сезімталдық өлшемі (SWI) сияқты түйін сөздер бойынша әдеби шолу жасалды. Шолу глиоманың қатерлі ісігін бағалау үшін молекулалық диагностика мен МРТ-ның мүмкіндіктерін қарастыратын 45 әдеби дереккөздердің талдау нәтижелерін қамтиды.*

Нәтижелер: *Бұл әдебиеттер шолуында глиомаларды диагностикалаудың ағымдағы тәсілдерінің өзектілігі көрсетілген, әртүрлі қатерлілік дәрежелері мен IDH мутациялық статусы MR кескіндерінде соның ішінде орналасу, сигнал және күшею паттеріндегі айырмашылықтармен байланысты бірегей мүмкіндіктер көрсетеді. (DTI) және (DWI) тіндердің микроқұрылымын бағалау үшін МРТ мүмкіндіктерін кеңейтіп, ісік сипаттамасын дәлірек анықтауға мүмкіндік береді. МРТ морфологиялық ерекшеліктерін, ADC параметрлерін және DTI параметрлерін біріктіретін зерттеулер глиоманың болжамына инвазивті емес тәсілді ұсынады, диагностика мен терапияны жақсарту үшін бейнелеу әдістерін кешенді пайдаланудың маңыздылығын көрсетеді.*

Қорытынды: *Магнитті-резонансты бейнелеуді қолдану глиомалардың морфологиялық және метаболикалық сипаттамаларын дәлірек анықтауға мүмкіндік береді, бұл дәрігерлерге дәл болжамды бағалауға және тиісті емдеу стратегиясын таңдауды тиімді етеді.*

Түйінді сөздер: *глиома, IDH мутациясы, IDH жабайы түрі, МРТ, магниттік резонанстық спектроскопия, ADC, DWI, DTI, DKI, SWI.*

АННОТАЦИЯ

СОВРЕМЕННЫЕ МЕТОДЫ ВИЗУАЛИЗАЦИИ В ОЦЕНКЕ СТЕПЕНИ ЗЛОКАЧЕСТВЕННОСТИ ГЛИАЛЬНЫХ ОПУХОЛЕЙ ГОЛОВНОГО МОЗГА: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *Глиомы представляют собой основную группу первичных опухолей центральной нервной системы и составляют около 80% от всех злокачественных новообразований головного мозга. Современные достижения в области молекулярной диагностики, включая идентификацию мутаций в гене изоцитратдегидрогеназы (IDH), открывают новые возможности для улучшения классификации глиом и понимания механизмов их развития. Мутации IDH, обнаруженные в значительной части глиом, связаны с лучшим прогнозом и представляют собой важный биомаркер, способствующий разработке целенаправленных терапевтических стратегий. Также важную роль играют методы диагностики, в частности магнитно-резонансная томография (МРТ), которые обеспечивают дополнительные возможности для оценки морфологических и биологических характеристик глиом, способствуя более точному определению степени злокачественности опухолей и их молекулярного профиля, что имеет ключевое значение для принятия решений о лечении.*

Цель исследования *– изучить возможности магнитно-резонансной томографии в оценке степени злокачественности глиальных опухолей головного мозга.*

Методы: *Проведен литературный обзор по ключевым словам: глиома, мутация IDH, дикий тип IDH, МРТ, магнитно-резонансная спектроскопия (MRS), аппарентный коэффициент диффузии (ADC), диффузионно-взвешенная визуализация (DWI), диффузионно-тензорная визуализация (DTI), диффузионное куртозное изображение (DKI), взвешенность по магнитной восприимчивости (SWI) в базах данных PubMed, BMC Medicine и Google Scholar. Обзор включает результаты анализа 45 литературных источников, рассматривающих диагностические возможности молекулярной диагностики и МРТ для оценки степени злокачественности глиом.*

Результаты: *В данном обзоре подчеркивается значимость современных подходов к диагностике глиом. Отмечается, что различные степени злокачественности и мутационный статус IDH ассоциируются с уникальными особенностями на МРТ-изображениях, включая различия в локализации, сигналах и паттернах усиления. DTI и DWI расширяют возможности МРТ для оценки микроструктуры ткани, позволяя точнее определять характеристики опухоли. Исследования, сочетающие морфологические характеристики МРТ, параметры ADC и DTI, предлагают неинвазивный подход к прогнозированию глиом, подчеркивая важность интегрированного использования методов визуализации для улучшения диагностики и терапии.*

Заключение: *Применение магнитно-резонансной томографии позволяет более точно определять морфологические и метаболические характеристики глиом в оценке степени злокачественности, позволяя врачам делать более точные прогностические оценки и выбирать наиболее подходящую стратегию лечения.*

Ключевые слова: *глиома, мутация IDH, дикий тип IDH, МРТ, магнитно-резонансная спектроскопия, ADC, DWI, DTI, DKI, SWI.*

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