

**QUANTITATIVE MRI BIOMARKERS IN GLIOBLASTOMA: AN UPDATED REVIEW ABOUT PHYSIOPATHOLOGY, WHO CNS5 CLASSIFICATION AND CLINICAL APPLICATIONS**

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**G**lioblastoma (GBM) is the most common primary malignant brain tumour and one of the most aggressive neoplasms of the central nervous system, with a median overall survival of approximately eight months. Over the past decade, significant progress has been made in understanding its underlying pathophysiology, paralleled by advances in magnetic resonance imaging (MRI) techniques. These include functional, metabolic, and microstructural imaging modalities that enable a more comprehensive characterisation of GBM through diverse physiological and biophysical biomarkers.

A prominent development in this context is radiomics, a high-throughput image analysis approach that extracts large volumes of quantitative features from conventional and advanced imaging. Radiomics offers a non-invasive avenue to interrogate tumour biology, providing valuable insights into prognosis, treatment response, molecular classification, tumour microenvironment, and the distinction between true progression and pseudoprogression.

Despite their potential, these advanced imaging techniques are not yet widely implemented due to infrastructure limitations and the complexity of post-processing. Moreover, consensus is lacking on which radiomic features are clinically actionable, and further validation in large, multicentre studies is required before their routine clinical integration.

This review aims to provide a comprehensive overview of glioblastoma imaging, with a particular focus on the most recent and clinically relevant applications of advanced MRI techniques and radiomic analysis. We summarise current evidence on the diagnostic, prognostic, and predictive utility of radiomics in GBM, to offer clinicians a practical understanding of emerging imaging biomarkers in neuro-oncology.

Keywords: Glioblastoma, radiomics, magnetic resonance imaging, spectroscopy, biomarkers.

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**КОЛИЧЕСТВЕННЫЕ МРТ-БИОМАРКЕРЫ ПРИ ГЛИОБЛАСТОМЕ: ОБНОВЛЕННЫЙ ОБЗОР ПАТОФИЗИОЛОГИИ, CNS5 КЛАССИФИКАЦИИ ВОЗ И КЛИНИЧЕСКОЕ ПРИМЕНЕНИЕ**

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**Г**лиобластома (GBM) является наиболее распространённой первичной злокачественной опухолью головного мозга и одной из самых агрессивных неоплазий центральной нервной системы, со средним показателем общей выживаемости около восьми месяцев. За последнее десятилетие достигнут значительный прогресс в понимании её патофизиологии, параллельно с развитием магнитно-резонансной томографии (МРТ). К ним относятся функциональные, метаболические и микроструктурные методы визуализации, которые позволяют более полно характеризовать глиобластому на основе различных физиологических и биофизических биомаркеров.

Одним из наиболее заметных достижений в этой области является радиомика – высокопроизводительный метод анализа изображений, позволяющий извлекать большие массивы количественных признаков из стандартных и современных методов визуализации. Радиомика открывает неинвазивные возможности для изучения биологии опухоли, предоставляя ценную информацию о прогнозе, ответе на лечение, молекулярной классификации, микроокружении опухоли, а также о различиях истинной прогрессии и псевдопрогрессии.

Несмотря на высокий потенциал, эти методы современной визуализации пока не получили широкого внедрения из-за инфраструктурных ограничений и сложности постобработки данных. Кроме того, отсутствует консенсус относительно того, какие радиомические признаки обладают клинической значимостью и необходима дальнейшая ее оценка в крупных многоцентровых исследованиях, прежде чем они смогут быть интегрированы в рутинную клиническую практику.

Цель данного обзора – представить всестороннюю характеристику методов визуализации глиобластомы, с особым акцентом на наиболее современные и клинически значимые применения новых методик МРТ и радиомического анализа. Мы обобщаем текущие данные о диагностической, прогностической и предиктивной ценности радиомики при глиобластоме, предлагая клиницистам практическое понимание новых биомаркеров визуализации в нейроонкологии.

**Ключевые слова:** глиобластома, радиомикология, магнитно-резонансная томография, спектроскопия, биомаркеры.

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**G**lioblastoma (GBM) is the most common primary malignant brain tumour in adults and is classified as a World Health Organization (WHO) grade 4 neoplasm due to its aggressive biological behavior and poor prognosis [1, 2]. Despite aggressive multimodal treatment – which typically involves maximal safe surgical resection followed by radiotherapy and concomitant/adjuvant chemotherapy with temozolomide – most patients experience disease recurrence within 6 to 9 months of initial therapy [3, 4]. Even with these therapeutic interventions, the median overall survival remains dismal at approximately eight months in many cohorts [3, 5-7].

In recent years, advanced magnetic resonance imaging (MRI) techniques have gained prominence for their role in improving GBM detection, tumor delineation, and response assessment. These methods extend well beyond traditional contrast enhancement and offer superior capabilities in characterizing tumor heterogeneity, distinguishing viable tissue, and guiding histologically relevant treatment planning [8, 9]. Such developments are especially relevant in the era of precision medicine, where noninvasive assessment of tumour biology can influence both diagnosis and treatment strategies.

Despite significant molecular and therapeutic advances in oncology, GBM remains an exception, with only incremental survival improvements over decades. Nonetheless, the growing understanding of GBM biology continues to inform targeted drug development and novel clinical trials [10, 11].

This review aims to present a comprehensive and up-to-date synthesis of glioblastoma pathophysiology, treatment, and diagnostic assessment, with a particular focus on imaging biomarkers. We emphasize how the 2021 WHO CNS5 classification integrates molecular insights into clinical practice and explore how imaging – especially advanced MRI techniques and radiomics – can serve as surrogate biomarkers for diagnosis, monitoring, and prognostication. The review is designed to serve clinicians and radiologists by outlining recent translational insights that bridge imaging science and therapeutic decision-making.

### ***Epidemiology.***

Glioblastomas are the most prevalent type of brain tumour, representing 49.1% of all primary malignant brain tumours and 14.3% of all primary brain and central nervous system (CNS) tumours in the United States. According to the Central Brain Tumor Registry of the United States (CBTRUS), the annual incidence is approximately 3.23 cases per 100,000 popu-

lation [5]. These tumours exhibit a notably aggressive clinical course, with a dismal five-year survival rate of 6.8% and a median overall survival time of approximately eight months [5].

Epidemiologically, glioblastomas predominantly affect adults, with a median age at diagnosis of 65 years, and they are 1.6 times more frequent in males than in females [5, 12]. Clinical outcomes tend to be significantly worse in patients over 65 years of age compared to younger cohorts, reflecting the influence of age-related factors on tumour biology and therapeutic response [13].

### ***Risk factors.***

The majority of glioma cases arise sporadically, without a documented family history or identifiable environmental trigger. However, approximately 5% of cases are linked to hereditary conditions, and 1-2% of adult glioma cases occur in association with Mendelian disorders or familial cancer syndromes such as Lynch syndrome, neurofibromatosis, tuberous sclerosis, and Li-Fraumeni syndrome [1, 12].

Among environmental exposures, ionising radiation remains the most consistent and well-established risk factor for gliomas. This carcinogenic effect is more pronounced in children, with a latency period of approximately 7-9 years between exposure and tumour development. Ionising radiation is primarily associated with an increased incidence of gliomas and meningiomas [14]. A structured summary of recognised risk factors is provided in Table 1.

A recent study (2023) examined the relationship between socioeconomic status (SES) and glioblastoma incidence. It demonstrated that individuals residing in areas with higher SES not only have a greater incidence of glioblastoma but also exhibit longer average survival times, potentially reflecting better access to healthcare resources and timely interventions [15]. Nevertheless, further systematic reviews and meta-analyses are needed to validate and contextualise these findings across broader populations.

Conversely, atopic conditions such as eczema, asthma, and allergic rhinitis have been inversely associated with glioma risk. Several epidemiological studies report a risk reduction of up to 30% in individuals with a history of allergies [14]. Although the underlying mechanism is not fully elucidated, one prevailing hypothesis suggests that chronic allergic inflammation may enhance immune surveillance, reducing the likelihood of tumour initiation [14, 16]. This immunological hypothesis is illustrated in Figure 1.

Glioblastoma is also linked to a prothrombotic state. Malignancy-induced hyperco-

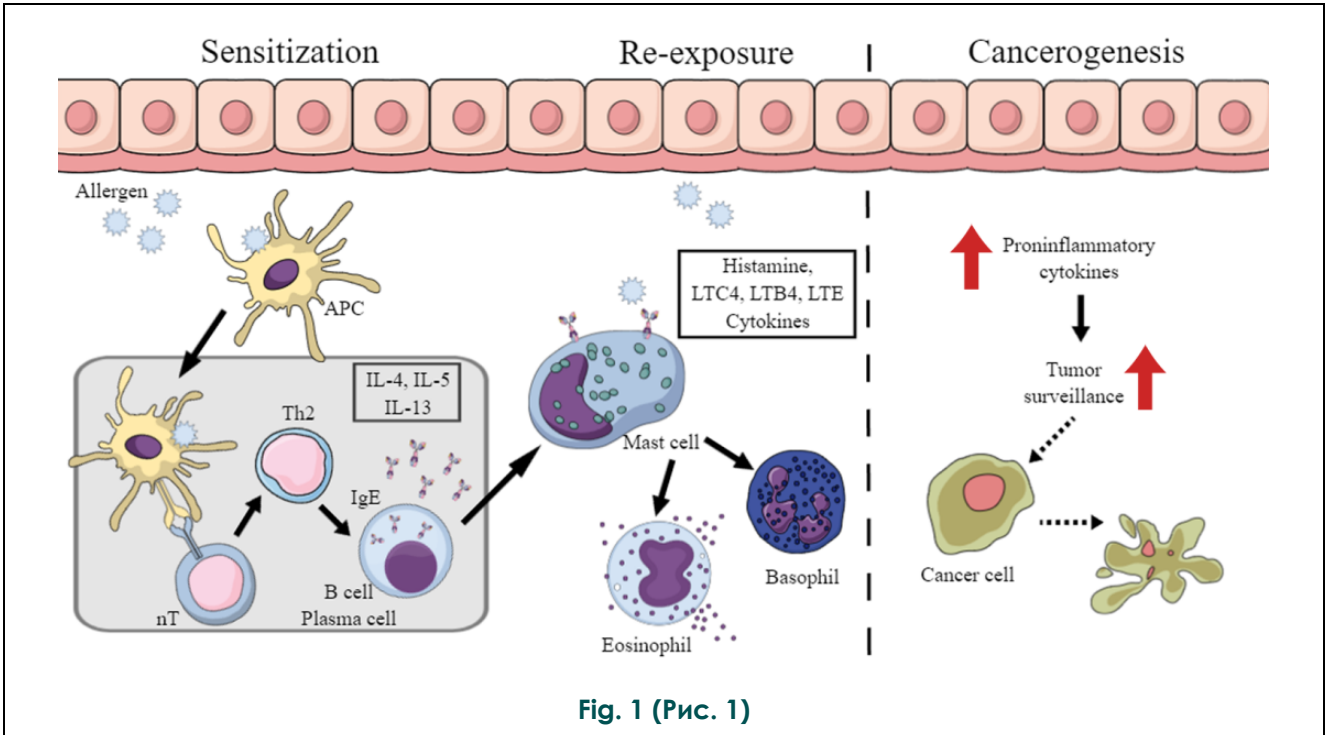


Fig. 1 (Рис. 1)

Fig. 1. Scheme.

a Inverse relationship between allergic conditions and the risk of developing GBM. Upon exposure to an allergen, immune cells may become sensitised to mount a more robust response upon subsequent exposure. This immunologic state is hypothesised to foster a pro-inflammatory cytokine milieu that enhances tumour immune surveillance (dashed lines), thereby potentially reducing the risk of glioblastoma development.

Рис. 1. Схема.

Обратная зависимость между аллергическими состояниями и риском развития глиобластомы. При контакте с аллергеном иммунные клетки подвергаются сенсибилизации, что обеспечивает мобилизацию более выраженного и направленного иммунного ответа при последующем воздействии того же антигена. Предполагается, что данное иммунологическое состояние способствует формированию провоспалительной цитокиновой микросреды, усиливающей противоопухолевый иммунный контроль (пунктирные линии), что потенциально может приводить к снижению вероятности развития глиобластомы..

Table №1. Risk factors associated with GBM.

Risk Factor	Significance
Exposure to Ionising Radiation	Strongest documented environmental risk factor
Family history of GBM	They represent 5% of total GBM cases.
Mendelian disorders or inherited syndromes	Accountable for 1-2% of adult cases of GBM
Male sex	1.6 more common in men than in women
Advanced age	The median age of diagnosis is 65 years.

agulability contributes to a significant risk of venous thromboembolism. The reported incidence of deep vein thrombosis (DVT) post-surgery ranges between 3% and 60%, depending on the type of prophylaxis employed. Moreover, the 12-month cumulative risk of pulmonary venous thromboembolism (PVT) reaches up to 20.8% in this population [17].

**Subventricular zone (SVZ).**

Emerging evidence indicates that neural stem cells (NSCs) residing within the subventricular zone (SVZ) may play a central role in the origin and progression of glioblastoma [18, 19]. The SVZ, anatomically located along the lateral walls of the lateral ventricles, is a recognized neurogenic niche in the adult human brain. NSCs in this region demonstrate key features of self-renewal, multipotency, and migratory capability, which may contribute to gliomagenesis.

One of the critical attributes of NSCs is their affinity for vascular structures and white matter tracts, facilitating their ability to migrate over long distances to different brain regions [18-20]. This characteristic is paralleled in glioma cell behaviour, as glioblastoma cells have been documented to infiltrate up to 7 cm from the primary tumour core [20].

Notably, glioblastomas located in close proximity to the SVZ exhibit more aggressive clinical and radiological features, including increased infiltration, multifocal presentation, and early recurrence. Recent studies confirm that SVZ involvement is an independent negative prognostic factor for both overall survival (OS) and progression-free survival (PFS) in patients with glioblastoma [18].

**Location of glioblastoma.**

Glioblastomas are primarily intraparenchymal tumours, with a predilection for the cerebral hemispheres. The frontal (23.6%) and temporal (17.4%) lobes are the most frequently affected regions, followed by the parietal (10.6%) and occipital (2.8%) lobes [1, 16, 21]. Less commonly, glioblastomas may involve the brainstem, cerebellum, or spinal cord [16].

A magnetic resonance imaging-based classification has been proposed to account for the heterogeneity of tumour localisation based on subventricular zone (SVZ) and cortical involvement, offering insights into the histogenetic and prognostic variability of glioblastoma [22]:

- Group I: Contrast-enhancing lesion extending from the atrium SVZ to the pia.
- Group II: Tumour in contact with the SVZ but not involving the cortex.
- Group III: Tumour invading the cortex and reaching the pia without contacting the SVZ.

- Group IV: Tumour sparing both the SVZ and cortex.

This classification is illustrated in Figure 2, highlighting the anatomical and potential prognostic distinctions.

Although glioblastoma is locally aggressive, metastatic dissemination is uncommon. Intracranial metastases are rare due to the typically short survival time of patients, which limits clinical detection [23, 24]. Similarly, extracranial metastases are highly uncommon, with an estimated incidence of 0.5-2%, and are usually associated with poor prognosis [25, 26]. In such cases, the median overall survival following metastatic diagnosis is approximately 6 ± 0.8 months [27].

**WHO CNS5 classification.**

The fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System (WHO CNS5), released in 2021, introduced pivotal changes that have transformed the diagnostic landscape of glioblastoma and other gliomas. These updates are the culmination of evolving molecular insights and were heavily informed by the recommendations of the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) [28].

Historically, the classification of gliomas relied predominantly on histopathological criteria, such as mitotic index, cellular atypia, necrosis, and microvascular proliferation. However, the WHO CNS5 system now adopts an integrated histo-molecular approach, combining microscopic features with genetic and epigenetic markers to provide a more biologically accurate and prognostically informative diagnosis [1].

One of the major conceptual shifts in the new classification is the reorganization of diffuse gliomas into distinct categories based on age and molecular lineage, primarily distinguishing adult-type diffuse gliomas from pediatric-type gliomas, and separating them from glioneuronal and neuronal tumors [2]. This age-based stratification acknowledges the unique biological behaviors and genetic alterations observed in pediatric versus adult tumors, despite histological similarities.

In WHO CNS5, the term “glioblastoma” is now reserved exclusively for IDH-wildtype astrocytic tumors. In contrast, IDH-mutant diffuse astrocytic tumors, previously designated across three categories – diffuse astrocytoma, anaplastic astrocytoma, and glioblastoma, IDH-mutant – are now unified under the singular diagnostic entity of astrocytoma, IDH-mutant, with WHO grade 2, 3, or 4 assigned based on histological and molecular features [2]. This revision eliminates the term “glioblastoma,

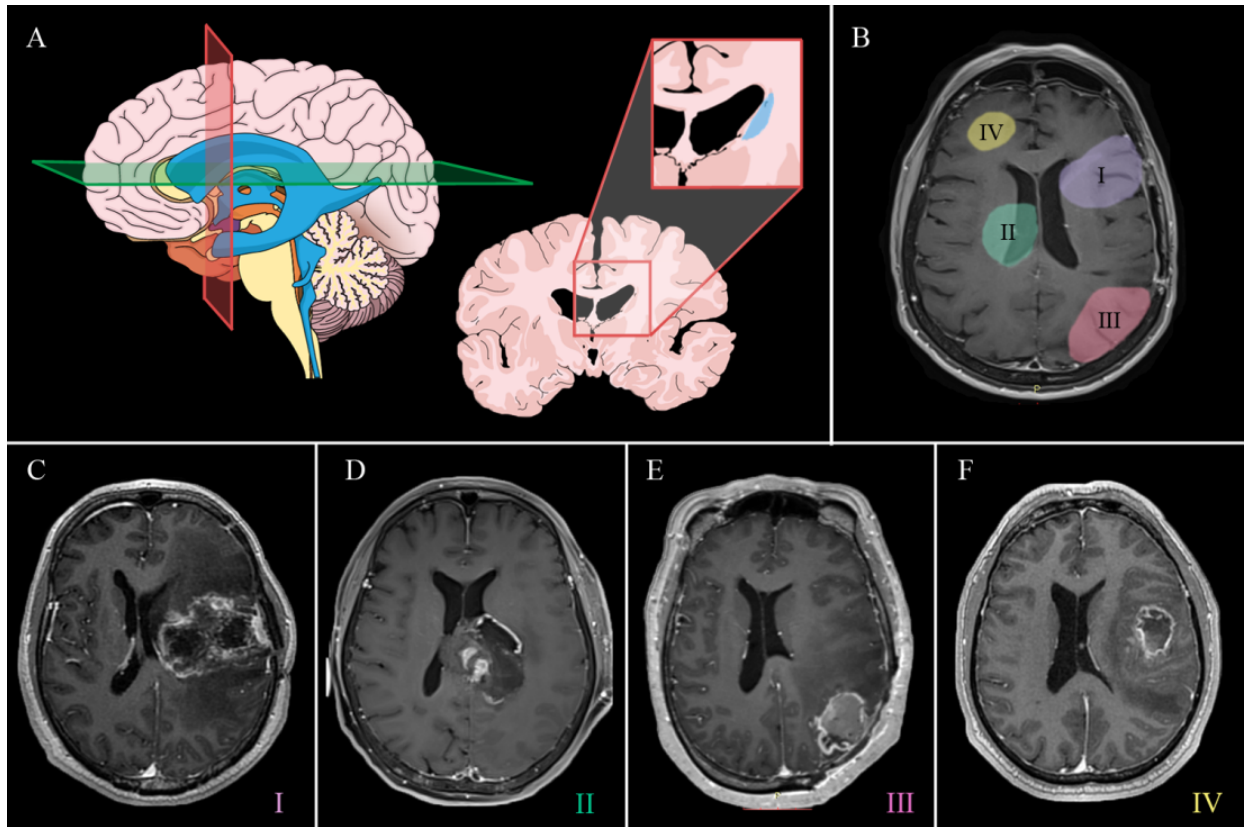


Fig. 2 (Рис. 2)

**Fig. 2. Magnetic resonance imaging-based classification of GBM.**

A – A sagittal section is used to visualise the subventricular zone (SVZ); the transverse section delineates the axial plane used in the following examples.

B – Schematic representation of the four GBM subtypes based on tumour location.

C – Group I: tumour extends from the SVZ to the cortex.

D – Group II: tumour contacts the SVZ but does not involve the cortex.

E – Group III: tumour invades the cortex but spares the SVZ.

F – Group IV: tumour respects both the SVZ and the cortex.

**Рис. 2. Классификация глиобластомы на основании данных магнитно-резонансной томографии.**

A – Сагиттальная плоскость используется для визуализации субвентрикулярной зоны; поперечный срез обозначает аксиальную плоскость, применяемую в последующих примерах.

B – Схематическое изображение четырёх подтипов глиобластомы в зависимости от локализации опухоли.

C – Группа I: опухоль распространяется от субвентрикулярной зоны к коре головного мозга.

D – Группа II: опухоль контактирует с субвентрикулярной зоной, но не затрагивает кору.

E – Группа III: опухоль проникает в кору, при этом субвентрикулярная зона остаётся интактной.

F – Группа IV: опухоль не затрагивает ни субвентрикулярную зону, ни кору.

IDH-mutant,” reflecting the distinct biology and more favorable prognosis associated with IDH mutations.

For adult-type IDH-wildtype diffuse astrocytic gliomas, the diagnosis of glioblastoma, IDH-wildtype (CNS WHO grade 4) can now be rendered even in the absence of classical histological hallmarks such as necrosis or microvascular proliferation, provided that at least one of the following three molecular features is present:

1. Combined gain of chromosome 7 and loss of chromosome 10 (+7/-10).
2. TERT promoter mutation.
3. EGFR gene amplification [2, 28].

These molecular markers have been shown to confer a poor prognosis comparable to histologically defined glioblastoma, thereby justifying their incorporation into diagnostic criteria even in morphologically ambiguous cases [29]. This shift reflects the broader trend in neuro-oncology towards molecularly driven classification, enhancing the precision of diagnosis and paving the way for more personalized treatment strategies.

The WHO CNS5 classification is not only diagnostically transformative but also clinically actionable, influencing therapeutic decisions and eligibility for clinical trials. As such, understanding its structure and implications is crucial for radiologists, pathologists, and neuro-oncologists involved in the management of gliomas.

#### ***Imaging of glioblastoma.***

Modern neuroimaging plays a pivotal role in the diagnosis, treatment planning, and follow-up of glioblastoma (GBM). Beyond its diagnostic utility, imaging is now central to understanding the tumor’s underlying biology, supporting a more tailored and noninvasive clinical approach. A wide range of imaging techniques is currently available to interrogate GBM from multiple dimensions – including structural, functional, hemodynamic, metabolic, and microstructural perspectives. These modalities enable comprehensive assessments that are critical not only for tumor detection and classification but also for therapy monitoring and evaluation of treatment response [30, 31].

In recent years, there has been a paradigm shift in the radiological evaluation of glioblastoma, moving from traditional qualitative assessments to advanced quantitative imaging. Conventional magnetic resonance imaging (MRI) sequences, such as T1-weighted, T2-weighted, FLAIR, and post-gadolinium contrast enhancement, remain the standard for tumor visualization and surgical planning. However, they are limited in their ability to capture the full biological complexity of GBM, particularly

in distinguishing true tumor progression from pseudoprogression or radiation necrosis.

To address these limitations, a growing number of advanced MRI techniques have been integrated into neuro-oncological imaging protocols. These include diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), magnetic resonance spectroscopy (MRS), and diffusion tensor imaging (DTI). Together, these sequences offer insights into tumor cellularity, vascularity, metabolic activity, and infiltration patterns – factors that are increasingly recognized as critical for prognosis and treatment stratification [8, 32].

Moreover, the rise of radiomics and radiogenomics has introduced new possibilities in glioblastoma imaging. These data-driven approaches extract high-dimensional features from imaging datasets and correlate them with molecular and clinical outcomes. As research in this field evolves, radiomics may soon serve as a bridge between radiology and genomics, enabling virtual biopsies and precision diagnostics.

Given this context, the following subsections will provide a detailed exploration of conventional and advanced MRI modalities in glioblastoma, followed by a review of MR spectroscopy, DTI, and radiomics applications. Figure 3 will illustrate conventional sequences and figures 4 and 5 will present schematic representations and clinical examples of advanced imaging techniques.

Abbreviations: ASL, arterial spin labeling; DCE, dynamic contrast-enhanced; DSC, dynamic susceptibility contrast; rCBV, relative cerebral blood volume; rCBF, relative cerebral blood flow; Cho, choline; NAA, N-acetylaspartate; mI/Cr, myo-inositol/creatine; P, pure isotropic diffusion; Q, pure anisotropic diffusion; L, total magnitude of the diffusion tensor; CL, linear tensor; CP, planar tensor; CS, spherical tensor; RA, relative anisotropy; RD, radial diffusivity; AD, axial diffusivity; FA, fractional anisotropy.

#### ***Conventional magnetic resonance imaging.***

Conventional magnetic resonance imaging (MRI) remains the cornerstone for the initial diagnosis, surgical planning, and monitoring of glioblastoma (GBM). With its high spatial resolution and excellent tissue contrast, MRI provides critical insights into both tumor morphology and peritumoral changes [22, 23]. The routine MRI protocol for glioma evaluation typically includes axial T1-weighted (pre- and post-gadolinium), T2-weighted, and fluid-attenuated inversion recovery (FLAIR) sequences, which together delineate tumor boundaries, surrounding edema, and local infiltration [34, 35].

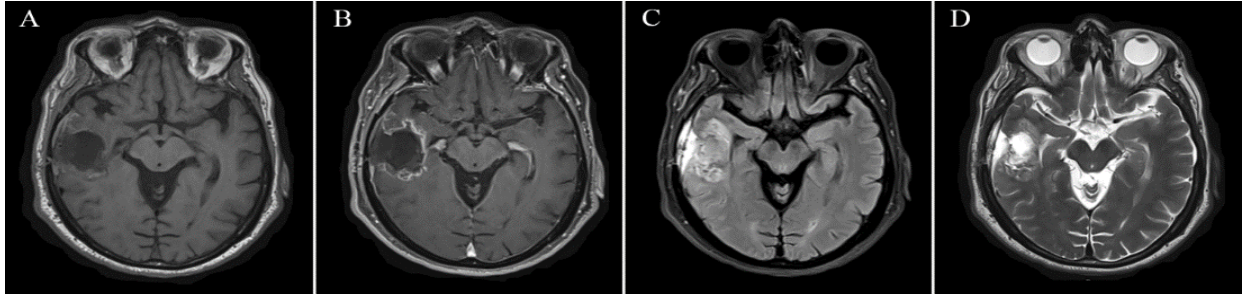


Fig. 3 (Рис. 3)

**Fig. 3. MRI. Conventional MRI techniques routinely used for brain tumour assessment.**

- A – T1-weighted image without contrast.
- B – T1-weighted image post-contrast administration.
- C – Fluid-attenuated inversion recovery (FLAIR) image.
- D – T2-weighted image.

**Рис. 3. МРТ. Стандартные режимы магнитно-резонансной томографии, регулярно используемые при оценке опухолей головного мозга.**

- А – T1-взвешенное изображение без контрастного усиления.
- В – T1-взвешенное изображение после введения контрастного вещества.
- С – Изображение с подавлением сигнала от жидкости (FLAIR, fluid-attenuated inversion recovery).
- Д – T2-взвешенное изображение.

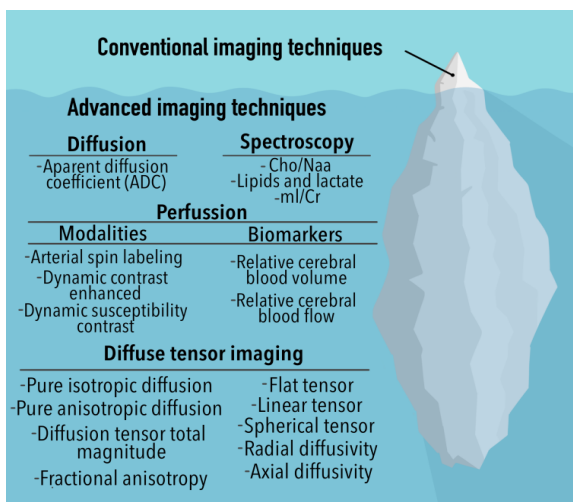


Fig. 4 (Рис. 4)

**Fig. 4. Scheme.**

Conventional versus advanced imaging techniques in GBM characterisation. The diagram contrasts standard qualitative MRI techniques (above the grey line) with advanced quantitative methods (below the line).

**Рис. 4. Схема.**

Традиционные и передовые методы визуализации при исследовании глиобластомы. На схеме показаны стандартные качественные технологии МРТ (выше серой линии) и передовые количественные технологии (ниже линии).

On conventional sequences, GBM characteristically presents as an ill-defined, heterogeneously enhancing mass with irregular margins. Intratumoral features often include central necrosis, cystic changes, hemorrhagic components at various stages, fluid-debris levels, and flow voids reflecting prominent vasculature [1, 9]. These heterogeneous elements are consistent with the aggressive and infiltrative nature of the tumor.

Several morphometric parameters derived from conventional imaging have been correlated with prognosis and treatment response. These include the rim width, contrast enhancement surface regularity, residual tumor volume (RTV), and extent of resection (EOR). Such metrics offer useful surrogate indicators of disease burden and surgical success [34].

Gadolinium-enhanced T1-weighted imaging remains the gold standard for contrast evaluation in GBM. Figure 3 illustrates typical appearances of GBM using standard sequences, including T1-weighted, T2-weighted, and FLAIR, which highlight different tumor components and their surrounding tissue environment [1, 35].

Despite its central role, conventional MRI has limitations – particularly in differentiating between tumor progression, pseudoprogression, and pseudoresponse. The widely adopted Response Assessment in Neuro-Oncology (RA-

NO) criteria rely heavily on imaging changes in contrast enhancement. However, contrast alterations may not reliably reflect true biological progression, especially in the early post-treatment period (up to 12 weeks) [34]. For instance, pseudoresponse, seen with antiangiogenic therapies, may mimic tumor regression by decreasing contrast enhancement due to vascular normalization, while pseudoprogression may simulate tumor growth through therapy-induced inflammation [36].

Given these interpretative challenges, there is growing consensus on the need for adjunctive imaging methods that provide functional, cellular, and metabolic data. Advanced MRI modalities and positron emission tomography (PET) are increasingly employed to overcome these diagnostic ambiguities by capturing the biological activity of the tumor rather than its anatomic appearance alone [37].

#### ***Advanced Magnetic Resonance Imaging Biomarkers in Glioblastoma.***

Over the past two decades, magnetic resonance imaging has evolved from a purely anatomical tool into a multifaceted platform for capturing physiological, metabolic, and molecular features of glioblastoma (GBM). Advanced MRI techniques now offer a noninvasive window into tumor biology, providing functional data that complements histological analysis and assists in diagnosis, risk stratification, and treatment planning [38].

Figure 4 schematically represents the distinction between conventional MRI sequences and advanced imaging biomarkers, highlighting that conventional modalities constitute only the visible "tip of the iceberg" in brain tumor imaging.

#### ***Apparent diffusion coefficient.***

The apparent diffusion coefficient (ADC) quantifies water molecule diffusivity within brain tissues and is derived from diffusion-weighted imaging (DWI). In glioblastoma, low ADC values are indicative of high cellularity and restricted diffusion, whereas elevated ADC values suggest vasogenic edema or necrosis associated with blood-brain barrier disruption [39-41].

Preoperative ADC has emerged as an independent adverse prognostic marker, correlating with MGMT promoter methylation status and overall survival, regardless of age, performance status, or resection volume [41].

Notably, ADC mapping also aids in distinguishing true tumor progression from pseudoprogression. Hein et al. demonstrated that mean ADC values in newly enhancing lesions were significantly lower in progression compared to pseudoprogression ( $p < 0.006$ ) [42]. Other studies confirmed that recurrent tumors

have markedly lower minimum ADC values compared to radiation-induced effects, allowing improved interpretation of ambiguous post-treatment changes [42, 43].

#### ***Perfusion-weighted Imaging.***

Perfusion-weighted imaging (PWI) techniques evaluate cerebral hemodynamics by quantifying blood volume, flow, and vessel permeability – parameters critical for understanding tumor angiogenesis. While conventional T1 post-contrast imaging reflects vessel leakiness, PWI offers a deeper insight into microvascular architecture [44, 45].

Among PWI modalities, dynamic susceptibility contrast (DSC), dynamic contrast-enhanced imaging (DCE), and arterial spin labeling (ASL) are widely utilized in neurooncology [45, 46].

Figure 5 demonstrates perfusion-derived curves and parametric maps in a patient with GBM, illustrating differences in relative cerebral tumor volume (rCTV) and cerebral blood volume (rCBV) between viable tumor tissue and normal brain. PWI is instrumental in monitoring antiangiogenic treatment response and may also guide biopsy targeting in non-enhancing tumor regions.

#### ***Magnetic resonance spectroscopy.***

Magnetic resonance spectroscopy (MRS) captures in vivo metabolic profiles, detecting chemical compounds that provide insight into tumor cell turnover, inflammation, and neuronal integrity [47, 48]. Key metabolites include:

- N-acetyl aspartate (NAA) – a marker of neuronal integrity (reduced in GBM).
- Choline (Cho) – elevated due to increased membrane turnover in glial proliferation.
- Myo-inositol – reflects glial activation.
- Lactate – associated with anaerobic glycolysis and inflammation [34, 48].

The Cho/NAA ratio has demonstrated prognostic utility, correlating with survival outcomes and responsiveness to antiangiogenic therapy ( $p < 0.028$ ) [49].

Furthermore, MRS uniquely allows the noninvasive detection of 2-hydroxyglutarate (2HG), an oncometabolite produced by IDH1/2-mutant gliomas. While these mutations lack definitive radiologic signatures, 2HG detection via MRS could soon be incorporated into diagnostic workflows aligned with the WHO CNS classification system [34, 50-52].

#### ***Diffusion Tensor Imaging and Biomarkers.***

Diffusion tensor imaging (DTI) extends traditional DWI by modeling the directionality of water diffusion, yielding a range of microstructural metrics applicable to tumor charac-

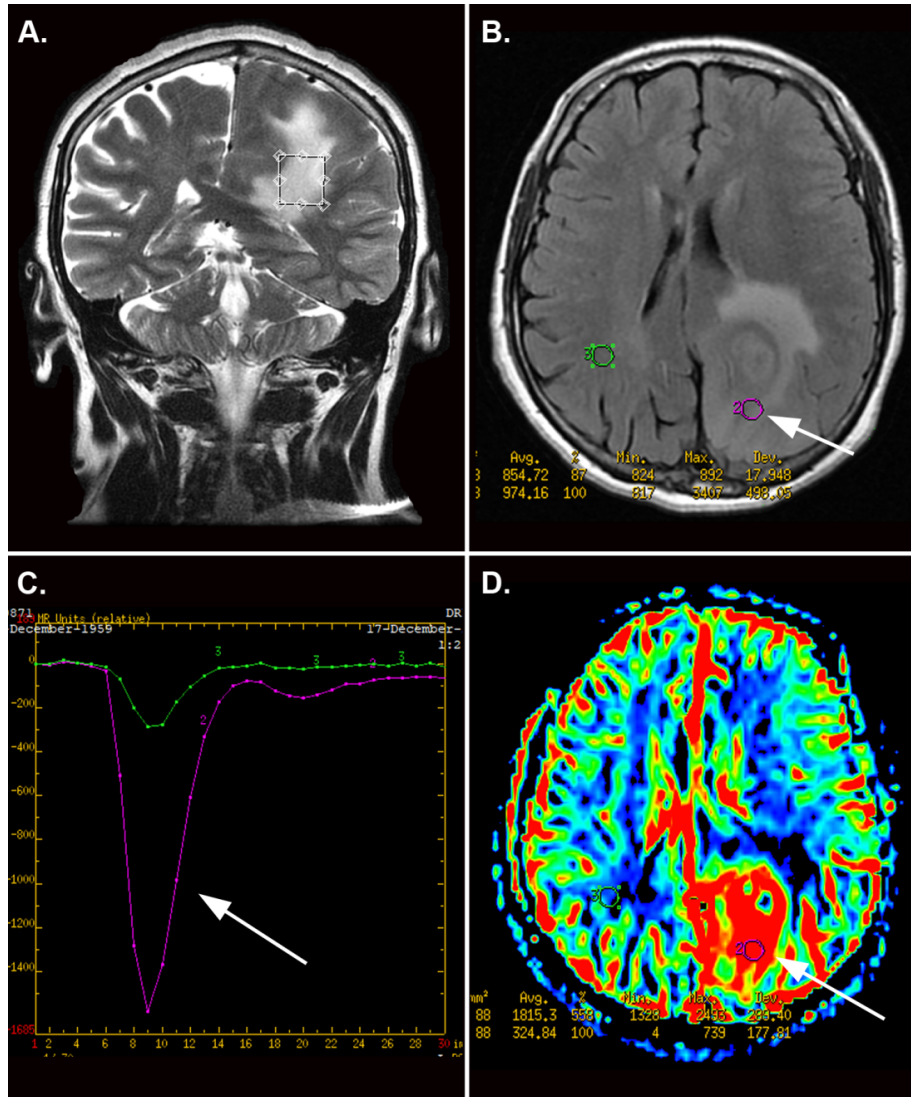


Fig. 5 (Рис. 5)

**Fig. 5. MRI. Conventional and perfusion-weighted imaging (PWI) in a patient with GBM.**

A – Coronal T2-weighted image.

B – Axial FLAIR image showing a viable tumour region (purple circle, white arrow) and contralateral normal tissue (green circle).

C – Perfusion curves from both regions, highlighting decreased perfusion in the tumour.

D – Colour intensity map from PWI indicating elevated relative tumour cerebral volume (rCTV), with a 5.58-fold increase compared to contralateral normal tissue. The rCBV of normal brain tissue is set as 100%.

**Рис. 5. МРТ. Традиционное и перфузионно-взвешенное изображение (PWI) у пациента с глиобластомой.**

A – Корональная плоскость, T2-взвешенное изображение.

B – Аксиальное FLAIR-изображение, показывающее жизнеспособный участок опухоли (фиолетовый круг, белая стрелка) и контралатеральную нормальную ткань (зелёный круг).

C – Кривые перфузии из обеих областей, демонстрирующие снижение перфузии в опухоли.

D – Карта интенсивности цвета, полученная с помощью PWI, указывающая на увеличение относительного объёма мозга опухоли (rCTV) в 5,58 раза по сравнению с контралатеральной нормальной тканью. rCBV нормальной ткани мозга принят за 100%.

terization [53, 54].

DTI-derived parameters include:

- Fractional anisotropy (FA) – reflects white matter tract integrity.
- Mean diffusivity (MD), axial (AD) and radial diffusivity (RD) – assess tissue density and demyelination.
- Isotropic/anisotropic components (p/q) and geometric descriptors (Cl, Cp, Cs, RA, L) – help define tumor and peritumoral architecture [34, 55].

These biomarkers support differentiation between GBM, metastases, abscesses, and normal tissue. A recent study demonstrated that low FA values (<25%) in peritumoral edema are linked with reduced survival (7-12 months), while higher FA values overlapping with contralateral white matter predicted prolonged survival exceeding 36 months [56]. Additionally, whole-brain DTI metrics have been integrated into machine learning models for glioblastoma diagnosis and molecular subtyping [55].

#### ***Radiomics in glioblastoma.***

Radiomics has emerged as a powerful paradigm in neuro-oncologic imaging, leveraging high-throughput computational methods to extract quantitative features from conventional and advanced imaging modalities [57]. These features – often imperceptible to the human eye – can reflect underlying tumor biology, including heterogeneity, cellularity, angiogenesis, and metabolic status. The foundational hypothesis of radiomics posits that imaging-derived phenotypes mirror biological and molecular processes within tumor tissue [58, 59].

Radiomics is generally categorized into two complementary approaches:

- Feature-based radiomics, in which predefined mathematical descriptors are used to quantify tumor morphology, texture, and intensity patterns;
- Deep-learning-based radiomics, where convolutional neural networks autonomously learn features directly from imaging data, often surpassing traditional models in prediction tasks [60].

In glioblastoma, radiomics plays a pivotal role across multiple clinical scenarios. It supports the noninvasive characterization of intratumoral spatial heterogeneity, facilitates the prediction of molecular markers such as IDH mutation and MGMT methylation status, and improves discrimination between true progression and pseudoprogression – a longstanding challenge in neuro-oncology [57, 61]. Moreover, radiomic signatures have been proposed as prognostic indicators, correlating with overall survival and treatment response.

Recent studies also highlight radiomics'

potential in identifying immune cell infiltration patterns within the tumor microenvironment. This information is crucial for predicting responsiveness to emerging immunotherapies. Additionally, large-scale multi-institutional datasets have begun to validate radiomic models in external cohorts, a critical step toward clinical translation [62].

Table 2 provides a comparative overview of key radiomics studies in GBM, including the imaging modalities used, targeted clinical outcomes, extracted features, and cohort sizes. These data illustrate the growing applicability of radiomics in precision neuro-oncology and underscore the shift toward imaging-based biomarkers that supplement histopathologic and molecular data.

#### ***Limitations of Imaging Biomarkers and Radiomics in Glioblastoma.***

Despite the promising insights offered by radiomics and advanced MRI biomarkers, several limitations hinder their widespread clinical adoption. A primary concern is the prolonged and complex post-processing pipeline required for many advanced imaging techniques, which may limit routine implementation in time-sensitive clinical settings.

Moreover, the clinical relevance of many extracted imaging features remains uncertain. Radiomics studies vary significantly in methodology, software platforms, and feature extraction algorithms, resulting in heterogeneous and non-reproducible datasets. For instance, while some studies evaluate hundreds to thousands of features, only a small fraction demonstrate statistical or clinical significance. A review of radiomic analyses in GBM found that only 7.25% of features were ultimately deemed clinically useful, and in one study, this figure dropped to as low as 0.04% [63].

Furthermore, the integration of multimodal imaging biomarkers continues to face challenges. In 2006, Peña et al. highlighted that the relationships among diffusion tensor imaging (DTI) metrics in brain tumor evaluation remained poorly understood [64]. Although subsequent work by Cortez-Conradts et al. (2015) examined the correlation structure among DTI-derived metrics in GBM, it did not explore their associations with metabolic data obtained from magnetic resonance spectroscopy (MRS) [55]. More recently, Flores-Álvarez et al. (2020) demonstrated significant correlations between DTI parameters and MRS-derived metabolite ratios in selected tumor regions, with over 50% of correlation coefficients showing meaningful relationships [34]. This reinforces the importance of integrated, region-specific imaging analyses in understanding tumor biology.

**Table №2. A selection of modern radiomic models for the evaluation of GBM.**

Study	Radiological sequence of interest	Description	Clinical Application	Radiomics used / extracted	Number of patients
Shim et al., 2021(79)	T1w1, DSC-MRI, FLAIR	Quantitative measurements of tumour perfusion to predict recurrence of GBM. They differentiate distantly from local recurrence.	Early identification of the likelihood of recurrence may lead to earlier interventions or modifications to the treatment plan.	32 / 1702	192
Nuechterlein et al., 2021(63)	T1w, TICE, T2w, FLAIR	They targeted feature extraction to predict the survival-associated prognosis, subdividing patients into two subgroups accordingly.	Risk stratification has an impact on patient care, allowing decision making, such as surgical management, in cases of recurrence, suggesting clinical trials.	15/35340	46
Yan et al., 2020 (80)	T1w, T2w, FLAIR DSC-MRI, DTI-MRI	Radiomics use to demonstrate distinct characteristics in areas of potential subsequent progression on preoperative MRI.	Identifying tumour progression sites provides a direction for future studies and treatment goals.	112/294	57
Choi et al., 2020 (81)	T1w, TICE, T2w, FLAIR	Based on different radiomics, patients were stratified into three subtypes that differed significantly in prognosis.	Radiomic subtypes could serve as imaging biomarkers for prognosis, as well as therapeutic strategies.	7/478	144
Park et al., 2020 (82)	T2w, FLAIR, T1w, DWI, T1CE, DSC-MRI	Developing a radiomic model to improve the prognosis in glioblastoma	The tool to estimate the survival probability at 1-2 years can help guide therapeutic strategies.	6/1618	216
Le et al., 2020 (83)	T1w, T1CE, T2w, FLAIR	Investigated the role of magnetic resonance characteristics and radiomics in predicting the MGMT genotype in patients with wild-type IDH1 GBM	Predicting the promotor status of MGMT may be beneficial in the primary diagnosis and treatment plan for patients with wild-type GBM IDH1	9/704	53
Binder et al., 2019 (84)	T1w, T1CE, T2w, DWI (ADC, FA, AD, RD), DSC-MRI (rCBV, PH, PSR)	Demonstrated that glioblastoma expressing EGFR A289 mutants exhibits invasive features and is associated with shorter survival in patients and mice.	These results serve to highlight the complexity of the EGFR signalling cascade and the nuances of the ECD pathway in the context of cancer.	299/2104	396
Li et al., 2019 (85)	T1w, T1CE, T2w	Identify a PTEN-predictive radiomic signature and assess the predictive efficiency of this signature.	The radiomic approach could potentially be a non-invasive surrogate for gene detection and further help in patient-tailored therapies.	6/862	109

Abbreviations: T1CE, T1-weighted contrast enhancement imaging, MGMT, O6-methylguanine-DNA methyltransferase, EGFR, epidermal growth factor receptor, ECD, extracellular domain, PTEN, phosphatase and tensin homologue, T1w, T1-weighted imaging; T2w, T2-weighted imaging, DSC, dynamic susceptibility contrast, FLAIR, fluid-attenuated inversion recovery, DWI, diffusion-weighted imaging, AD, axial diffusivity; ADC, apparent diffusion coefficient, DTI, diffuse tensor imaging, FA, fractional anisotropy, rCBV, relative blood volume, PSR, percentage signal recovery, IDH, isocitrate dehydrogenase, PH, peak height, PSR, percentage signal recovery.

In sum, although radiomics and quantitative MRI biomarkers hold considerable promise, standardization of acquisition protocols, robust cross-validation of predictive models, and external validation in multicenter cohorts are urgently needed to facilitate their integration into personalized glioblastoma management.

**Future Directions in Glioblastoma Imaging.**

The future of glioblastoma imaging is poised for significant advancement through the integration of emerging noninvasive technologies that enable in vivo tissue characterization. Among these, advanced diffusion-based techniques such as Diffusion Kurtosis Imaging (DKI) and Vascular, Extracellular, and Restricted Diffusion for Cytometry in Tumors (VERDICT) MRI are gaining traction as promising tools to assess microstructural complexity, tumor heterogeneity, and infiltration patterns in gliomas [65-68]. These techniques offer complementary information beyond the Gaussian assumptions of traditional diffusion-weighted imaging, enhancing the ability to delineate tumor margins and detect infiltrative tumor zones that are otherwise radiologically occult.

Simultaneously, metabolic imaging is gaining relevance in the context of molecular diagnostics. Isocitrate dehydrogenase (IDH) mutations, a hallmark of lower-grade gliomas and a subset of GBMs, induce a neomorphic enzymatic function that results in the accumulation of 2-hydroxyglutarate (2HG). The presence of 2HG is now detectable in vivo using proton magnetic resonance spectroscopy (<sup>1</sup>H-MRS), facilitating noninvasive genotyping and early prediction of therapeutic response [69-71].

Although <sup>1</sup>H-MRS has been extensively studied using metabolite ratios such as choline/N-acetylaspartate (Cho/NAA) and lipids/lactate, its broader clinical integration requires standardized thresholds for tumor classification and response evaluation [49, 72].

Recent advances have expanded the scope of MR spectroscopy to include novel nuclei, such as <sup>31</sup>P, <sup>23</sup>Na, and <sup>13</sup>C, offering deeper biochemical insights into GBM biology.

- <sup>31</sup>P MRS quantifies phosphomonoesters (PMEs) and phosphodiesteres (PDEs), associated with phospholipid turnover. Elevated PME levels have been linked to tumor cell proliferation and recurrence in GBM [73, 74].

- <sup>23</sup>Na MRI has shown promise in correlating with IDH mutation status, accurately classifying tumor grade, and predicting survival outcomes [75, 76].

- Hyperpolarized <sup>13</sup>C MRI, particularly using [1-<sup>13</sup>C] pyruvate, allows visualization of lac-

tate and bicarbonate metabolism within tumor tissue. This technique offers the potential to detect early treatment response prior to anatomical changes and is under active clinical investigation (Fig. 2) [77, 78, 79, 80].

As these innovations mature, the future of GBM imaging lies in multiparametric integration, combining anatomical, microstructural, and metabolic biomarkers. Such integration may significantly improve personalized treatment strategies and real-time monitoring of disease progression and therapeutic efficacy.

**Conclusions.**

The future of neuroradiological practice in the management of brain tumors, particularly glioblastoma, is poised to be transformed by the integration of advanced diagnostic tools – many of which rely on sophisticated post-processing of magnetic resonance imaging (MRI) data. These technologies are expected to enable a more personalized diagnostic approach, tailored to the molecular and structural features of individual tumors.

Current quantitative MRI biomarkers, including diffusion, perfusion, spectroscopy, and diffusion tensor imaging (DTI), will remain central to this evolution. Their continued development and clinical validation hold the potential to improve our understanding of glioma biology, facilitate more accurate tumor stratification, and provide robust metrics for monitoring treatment response and disease progression.

As imaging becomes increasingly intertwined with molecular and genetic data, the role of neuroradiology will expand beyond detection to encompass prognostication and therapeutic guidance – solidifying its role in precision oncology.

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**Conflicts of Interest.**

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## References:

1. Melhem JM, Detsky J, Lim-Fat MJ, Perry JR. Updates in IDH-Wildtype Glioblastoma. *Neurotherapeutics*. 2022;1-19.
2. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol*. 2021;23(8):1231-1251.
3. Goel NJ, Bird CE, Hicks WH, Abdullah KG. Economic implications of the modern treatment paradigm of glioblastoma: an analysis of global cost estimates and their utility for cost assessment. *J Med Econ*. 2021;24(1):1018-1024.
4. Norden AD, Korytowsky B, You M, et al. A Real-World Claims Analysis of Costs and Patterns of Care in Treated Patients with Glioblastoma Multiforme in the United States. *J Manag Care Spec Pharm*. 2019;25(4):428-436.
5. Ostrom QT, Cioffi G, Waite K, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2014-2018. *Neuro Oncol*. 2021;23(12 Suppl 2):iii1-iii105.
6. Au TH, Willis C, Reblin M, et al. Caregiver burden by treatment and clinical characteristics of patients with glioblastoma. *Support Care Cancer*. 2022;30(2):1365-1375.
7. Panje CM, Putora PM, Hundesberger T, et al. Impact of treatment decision algorithms on treatment costs in recurrent glioblastoma: a health economic study. *Swiss Med Wkly*. 2019;149:w20153.
8. Hu LS, Hawkins-Daarud A, Wang L, Li J, Swanson KR. Imaging of intratumoral heterogeneity in high-grade glioma. *Cancer Lett*. 2020;477:97-106.
9. John F, Bosnyák E, Robinette NL, et al. Multimodal imaging-defined subregions in newly diagnosed glioblastoma: impact on overall survival. *Neuro Oncol*. 2019;21(2):264-273.
10. Touat M, Idbaih A, Sanson M, Ligon KL. Glioblastoma targeted therapy: updated approaches from recent biological insights. *Ann Oncol*. 2017;28(7):1457-1472.
11. Kusaczuk M, Zhang X. Editorial: Targeting glioblastoma: Mechanisms of pathology and novel therapeutic strategies. *Front Mol Biosci*. 2023;10:1181398.
12. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol*. 2020;22(8):1073-1113.
13. Braun K, Ahluwalia MS. Treatment of Glioblastoma in Older Adults. *Curr Oncol Rep*. 2017;19(12):81.
14. Ostrom QT, Adel Fahmideh M, Cote DJ, et al. Risk factors for childhood and adult primary brain tumors. *Neuro Oncol*. 2019;21(11):1357-1375.
15. Gorenflo MP, Shen A, Murphy ES, Cullen J, Yu JS. Area-level socioeconomic status is positively correlated with glioblastoma incidence and prognosis in the United States. *Front Oncol*. 2023;13:1110473.
16. Davis ME. Epidemiology and Overview of Gliomas. *Semin Oncol Nurs*. 2018;34(5):420-429.
17. Roldán-Valadez E, Salazar-Landa M, Alva-López LF. [Pulmonary thromboembolism associated with glioblastoma multiforme: imaging diagnosis of a case and a review of the literature]. *Rev Neurol*. 2003;37(9):831-836.
18. Zhang GL, Wang CF, Qian C, Ji YX, Wang YZ. Role and mechanism of neural stem cells of the subventricular zone in glioblastoma. *World J Stem Cells*. 2021;13(7):877-893.
19. Lee JH, Lee JE, Kahng JY, et al. Human glioblastoma arises from subventricular zone cells with low-level driver mutations. *Nature*. 2018;560(7717):243-247.
20. Quiñones-Hinojosa A, Chaichana K. The human subventricular zone: a source of new cells and a potential source of brain tumors. *Exp Neurol*. 2007;205(2):313-324.
21. Khandwala K, Mubarak F, Minhas K. The many faces of glioblastoma: Pictorial review of atypical imaging features. *Neuroradiol J*. 2021;34(1):33-41.
22. Cisneros-Sanchez AK, Flores-Alvarez E, Melendez-Mier G, Roldan-Valadez E. Basic principles of mathematical growth modeling applied to high-grade gliomas: A brief clinical review for clinicians. *Neurol India*. 2018;66(6):1575-1583.
23. Goryaynov SA, Potapov AA, Ignatenko MA, et al. Glioblastoma metastases: a literature review and a description of six clinical observations. *Zh Vopr Neirokhir Im N N Burdenko*. 2015;79(2):33-43.
24. Zhang K, Yang Y, Zhuang J, Guo G, Chao X, Zhang Z. Intracranial dissemination of glioblastoma multiforme: a case report and literature review. *J Int Med Res*. 2022;50(7):3000605221112047.
25. Lah TT, Novak M, Breznik B. Brain malignancies: Glioblastoma and brain metastases. *Semin Cancer Biol*. 2020;60:262-273.
26. Kalokhe G, Grimm SA, Chandler JP, Helenowski I, Rademaker A, Raizer JJ. Metastatic glioblastoma: case presentations and a review of the literature. *J Neurooncol*. 2012;107(1):21-27.
27. Liu J, Shen L, Tang G, et al. Multiple extracranial metastases from glioblastoma multiforme: a case report and literature review. *J Int Med Res*. 2020;48(6):300060520930459.
28. Kurokawa R, Kurokawa M, Baba A, et al. Major Changes in 2021 World Health Organization Classification of Central Nervous System Tumors. *Radiographics*. 2022;42(5):1474-1493.
29. Gritsch S, Batchelor TT, Gonzalez Castro LN. Diagnostic, therapeutic, and prognostic implications of the 2021 World Health Organization classification of tumors of the central nervous system. *Cancer*. 2022;128(1):47-58.
30. Brindle KM, Izquierdo-García JL, Lewis DY, Mair RJ, Wright AJ. Brain Tumor Imaging. *J Clin Oncol*. 2017;35(21):2432-2438.
31. Mabray MC, Barajas RF, Jr., Cha S. Modern brain tumor imaging. *Brain Tumor Res Treat*. 2015;3(1):8-23.
32. Shukla G, Alexander GS, Bakas S, et al. Advanced magnetic resonance imaging in glioblastoma: a review. *Chin Clin Oncol*. 2017;6(4):40.
33. Ma X, Liu J. Predictive value of MRI features on glioblastoma. *Eur Radiol*. 2023.
34. Flores-Alvarez E, Anselmo Rios Piedra E, Cruz-Priego GA, Durand-Muñoz C, Moreno-Jimenez S, Roldan-Valadez E.

- Correlations between DTI-derived metrics and MRS metabolites in tumour regions of glioblastoma: a pilot study. *Radiol Oncol.* 2020;54(4):394-408.
35. Islam M, Wijethilake N, Ren H. Glioblastoma multiforme prognosis: MRI missing modality generation, segmentation and radiogenomic survival prediction. *Comput Med Imaging Graph.* 2021;91:101906.
36. Huang RY, Neagu MR, Reardon DA, Wen PY. Pitfalls in the neuroimaging of glioblastoma in the era of antiangiogenic and immuno/targeted therapy - detecting illusive disease, defining response. *Front Neurol.* 2015;6:33.
37. Abbasi AW, Westerlaan HE, Holtman GA, Aden KM, van Laar PJ, van der Hoorn A. Incidence of Tumour Progression and Pseudoprogression in High-Grade Gliomas: a Systematic Review and Meta-Analysis. *Clin Neuroradiol.* 2018;28(3):401-411.
38. Al-Okaili RN, Krejza J, Wang S, Woo JH, Melhem ER. Advanced MR imaging techniques in the diagnosis of intraaxial brain tumors in adults. *Radiographics.* 2006;26 Suppl 1:S173-189.
39. Baehring JM, Fulbright RK. Diffusion-weighted MRI in neuro-oncology. *CNS Oncol.* 2012;1(2):155-167.
40. Solar P, Hendrych M, Barak M, Valekova H, Hermanova M, Jancalek R. Blood-Brain Barrier Alterations and Edema Formation in Different Brain Mass Lesions. *Front Cell Neurosci.* 2022;16:922181.
41. Durand-Muñoz C, Flores-Alvarez E, Moreno-Jimenez S, Roldan-Valadez E. Pre-operative apparent diffusion coefficient values and tumour region volumes as prognostic biomarkers in glioblastoma: correlation and progression-free survival analyses. *Insights Imaging.* 2019;10(1):36.
42. Hein PA, Eskey CJ, Dunn JF, Hug EB. Diffusion-weighted imaging in the follow-up of treated high-grade gliomas: tumor recurrence versus radiation injury. *AJNR Am J Neuroradiol.* 2004;25(2):201-209.
43. Abdulla S, Saada J, Johnson G, Jefferies S, Ajithkumar T. Tumour progression or pseudoprogression? A review of post-treatment radiological appearances of glioblastoma. *Clin Radiol.* 2015;70(11):1299-1312.
44. Sidibe I, Tensaouti F, Roques M, Cohen-Jonathan-Moyal E, Laprie A. Pseudoprogression in Glioblastoma: Role of Metabolic and Functional MRI-Systematic Review. *Biomedicines.* 2022;10(2).
45. Gonçalves FG, Chawla S, Mohan S. Emerging MRI Techniques to Redefine Treatment Response in Patients With Glioblastoma. *J Magn Reson Imaging.* 2020;52(4):978-997.
46. van Dijken BRJ, van Laar PJ, Smits M, Dankbaar JW, Enting RH, van der Hoorn A. Perfusion MRI in treatment evaluation of glioblastomas: Clinical relevance of current and future techniques. *J Magn Reson Imaging.* 2019;49(1):11-22.
47. Weinberg BD, Kuruwa M, Shim H, Mullins ME. Clinical Applications of Magnetic Resonance Spectroscopy in Brain Tumors: From Diagnosis to Treatment. *Radiol Clin North Am.* 2021;59(3):349-362.
48. Lee EJ, Ahn KJ, Lee EK, Lee YS, Kim DB. Potential role of advanced MRI techniques for the peritumoural region in differentiating glioblastoma multiforme and solitary metastatic lesions. *Clin Radiol.* 2013;68(12):e689-697.
49. Roldan-Valadez E, Rios C, Motola-Kuba D, Matus-Santos J, Villa AR, Moreno-Jimenez S. Choline-to-N-acetyl aspartate and lipids-lactate-to-creatine ratios together with age assemble a significant Cox's proportional-hazards regression model for prediction of survival in high-grade gliomas. *Br J Radiol.* 2016;89(1067):20150502.
50. Garcia-Lezama M, Carrillo-Ruiz JD, Moreno-Jimenez S, Roldan-Valadez E. WHO CNS5 2021 includes specific mutations in gliomas that can be identified with MRI quantitative biomarkers. *Gac Med Mex.* 2023;159(2):161-168.
51. Brun-Vergara ML, Melkus G, Chakraborty S, et al. Diagnostic Accuracy of (1)H-MRS Using PRESS and MEGA-PRESS Techniques in the Preoperative Grading of Patients With Gliomas. *J Magn Reson Imaging.* 2025;61(6):2480-2488.
52. McHugh FA, Jiang J, Luton H, et al. 2-Hydroxyglutarate magnetic resonance spectroscopy for preoperative IDH molecular profiling - A review of the literature and real-world clinical translation in a busy neurosurgical neuro-oncology unit. *J Clin Neurosci.* 2025;133:111062.
53. Li Y, Zhang W. Quantitative evaluation of diffusion tensor imaging for clinical management of glioma. *Neurosurg Rev.* 2020;43(3):881-891.
54. Cortez-Conradis D, Favila R, Isaac-Olive K, Martinez-Lopez M, Rios C, Roldan-Valadez E. Diagnostic performance of regional DTI-derived tensor metrics in glioblastoma multiforme: simultaneous evaluation of p, q, L, Cl, Cp, Cs, RA, RD, AD, mean diffusivity and fractional anisotropy. *Eur Radiol.* 2013;23(4):1112-1121.
55. Cortez-Conradis D, Rios C, Moreno-Jimenez S, Roldan-Valadez E. Partial correlation analyses of global diffusion tensor imaging-derived metrics in glioblastoma multiforme: Pilot study. *World J Radiol.* 2015;7(11):405-414.
56. Flores-Alvarez E, Durand-Muñoz C, Cortes-Hernandez F, Muñoz-Hernandez O, Moreno-Jimenez S, Roldan-Valadez E. Clinical Significance of Fractional Anisotropy Measured in Peritumoral Edema as a Biomarker of Overall Survival in Glioblastoma: Evidence Using Correspondence Analysis. *Neurol India.* 2019;67(4):1074-1081.
57. Habib A, Jovanovich N, Hoppe M, et al. MRI-Based Radiomics and Radiogenomics in the Management of Low-Grade Gliomas: Evaluating the Evidence for a Paradigm Shift. *J Clin Med.* 2021;10(7).
58. Martin P, Holloway L, Metcalfe P, Koh ES, Brighi C. Challenges in Glioblastoma Radiomics and the Path to Clinical Implementation. *Cancers (Basel).* 2022;14(16).
59. Dedhia M, Germano IM. The Evolving Landscape of Radiomics in Gliomas: Insights into Diagnosis, Prognosis, and Research Trends. *Cancers (Basel).* 2025;17(9).
60. Lohmann P, Galldiks N, Kocher M, et al. Radiomics in neuro-oncology: Basics, workflow, and applications. *Methods.* 2021;188:112-121.
61. Park JE, Kickingereder P, Kim HS. Radiomics and Deep Learning from Research to Clinical Workflow: Neuro-Oncologic Imaging. *Korean J Radiol.* 2020;21(10):1126-1137.
62. Chilaca-Rosas MF, Garcia-Lezama M, Moreno-Jimenez S, Roldan-Valadez E. Diagnostic Performance of Selected MRI-Derived Radiomics Able to Discriminate Progression-Free and Overall Survival in Patients with Midline Glioma and the H3F3AK27M Mutation. *Diagnostics (Basel).* 2023;13(5).

63. Nuechterlein N, Li B, Feroze A, et al. Radiogenomic modeling predicts survival-associated prognostic groups in glioblastoma. *Neurooncol Adv.* 2021;3(1):vdab004.
64. Peña A, Green HA, Carpenter TA, Price SJ, Pickard JD, Gillard JH. Enhanced visualization and quantification of magnetic resonance diffusion tensor imaging using the p:q tensor decomposition. *Br J Radiol.* 2006;79(938):101-109.
65. Van Cauter S, Veraart J, Sijbers J, et al. Gliomas: diffusion kurtosis MR imaging in grading. *Radiology.* 2012;263(2):492-501.
66. Van Cauter S, De Keyzer F, Sima DM, et al. Integrating diffusion kurtosis imaging, dynamic susceptibility-weighted contrast-enhanced MRI, and short echo time chemical shift imaging for grading gliomas. *Neuro Oncol.* 2014;16(7):1010-1021.
67. Zerweck L, Wurtemberger U, Klose U, et al. Performance Comparison of Diffusion Kurtosis Imaging (DKI), Neurite Orientation Dispersion and Density Imaging (NODDI), and Diffusion Microstructure Imaging (DMI) in Predicting Adult-Type Glioma Subtype-A Pilot Study. *Cancers (Basel).* 2025;17(5).
68. Song D, Fan G, Chang M. Research Progress on Glioma Microenvironment and Invasiveness Utilizing Advanced Multi-Parametric Quantitative MRI. *Cancers (Basel).* 2024;17(1).
69. Choi C, Ganji SK, DeBerardinis RJ, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. *Nat Med.* 2012;18(4):624-629.
70. Pope WB, Prins RM, Albert Thomas M, et al. Non-invasive detection of 2-hydroxyglutarate and other metabolites in IDH1 mutant glioma patients using magnetic resonance spectroscopy. *J Neurooncol.* 2012;107(1):197-205.
71. Andronesi OC, Kim GS, Gerstner E, et al. Detection of 2-hydroxyglutarate in IDH-mutated glioma patients by in vivo spectral-editing and 2D correlation magnetic resonance spectroscopy. *Sci Transl Med.* 2012;4(116):116ra114.
72. Wang W, Hu Y, Lu P, et al. Evaluation of the diagnostic performance of magnetic resonance spectroscopy in brain tumors: a systematic review and meta-analysis. *PLoS One.* 2014;9(11):e112577.
73. Arnold DL, Emrich JF, Shoubbridge EA, Villemure JG, Feindel W. Characterization of astrocytomas, meningiomas, and pituitary adenomas by phosphorus magnetic resonance spectroscopy. *J Neurosurg.* 1991;74(3):447-453.
74. Peter SB, Nandhan VR. 31-Phosphorus Magnetic Resonance Spectroscopy in Evaluation of Glioma and Metastases in 3T MRI. *Indian J Radiol Imaging.* 2021;31(4):873-881.
75. Biller A, Badde S, Nagel A, et al. Improved Brain Tumor Classification by Sodium MR Imaging: Prediction of IDH Mutation Status and Tumor Progression. *AJNR Am J Neuroradiol.* 2016;37(1):66-73.
76. Shams Z, Dai J, Gosselink MWJ, et al. Interleaved Whole Brain (23)Na-MRI and (31)P-MRSI Acquisitions at 7 Tesla. *NMR Biomed.* 2025;38(3):e70012.
77. Park JM, Recht LD, Josan S, et al. Metabolic response of glioma to dichloroacetate measured in vivo by hyperpolarized (13)C magnetic resonance spectroscopic imaging. *Neuro Oncol.* 2013;15(4):433-441.
78. Park JM, Spielman DM, Josan S, et al. Hyperpolarized (13)C-lactate to (13)C-bicarbonate ratio as a biomarker for monitoring the acute response of anti-vascular endothelial growth factor (anti-VEGF) treatment. *NMR Biomed.* 2016;29(5):650-659.
79. Chekhonin I.V., Pogosbekyan E.L., Nikitin P.V., Batalov A.I., Bykanov A.E., Maryashev S.A., Pitskhelauri D.I., Zakharova N.E., Pronin I.N. Magnetic resonance relaxometry and diffusion-weighted imaging in Glioma grading and IDH1 mutational status assessment. *REJR.* 2022; 12(1):21-31. DOI: 10.21569/2222-7415-2022-12-1-21-31.
80. Tyurina A.N., Vikhrova N.B., Batalov A.I., Fadeeva L.M., Konakova T.A., Mertsalova M.P., Pronin I.N. Multivoxel 3D magnetic resonance spectroscopy and positron emission tomography with 11C-methionine in the preoperative diagnosis of high-grade gliomas (pilot study). *REJR.* 2020; 10(4):75-84. DOI:10.21569/2222-7415-2020-10-4-75-84.
81. Shim KY, Chung SW, Jeong JH, et al. Radiomics-based neural network predicts recurrence patterns in glioblastoma using dynamic susceptibility contrast-enhanced MRI. *Sci Rep.* 2021;11(1):9974.
82. Yan JL, Li C, van der Hoorn A, Boonzaier NR, Matys T, Price SJ. A Neural Network Approach to Identify the Peritumoral Invasive Areas in Glioblastoma Patients by Using MR Radiomics. *Sci Rep.* 2020;10(1):9748.
83. Choi SW, Cho HH, Koo H, et al. Multi-Habitat Radiomics Unravels Distinct Phenotypic Subtypes of Glioblastoma with Clinical and Genomic Significance. *Cancers (Basel).* 2020;12(7).
84. Park JE, Kim HS, Jo Y, et al. Radiomics prognostication model in glioblastoma using diffusion- and perfusion-weighted MRI. *Sci Rep.* 2020;10(1):4250.
85. Le NQK, Do DT, Chiu FY, Yapp EKY, Yeh HY, Chen CY. XGBoost Improves Classification of MGMT Promoter Methylation Status in IDH1 Wildtype Glioblastoma. *J Pers Med.* 2020;10(3).
86. Binder ZA, Thorne AH, Bakas S, et al. Epidermal Growth Factor Receptor Extracellular Domain Mutations in Glioblastoma Present Opportunities for Clinical Imaging and Therapeutic Development. *Cancer Cell.* 2018;34(1):163-177.e167.
85. Li Y, Liang Y, Sun Z, et al. Radiogenomic analysis of PTEN mutation in glioblastoma using preoperative multiparametric magnetic resonance imaging. *Neuroradiology.* 2019;61(11):1229-1237.