Review Article

Imaging Role in Diagnosis, Prognosis, and Treatment Response Prediction Associated with High-grade Glioma

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Abstract

Background: Glioma is one of the most drug and radiation-resistant tumors. Gliomas suffer from inter- and intratumor heterogeneity which makes the outcome of similar treatment protocols vary from patient to patient. This article is aimed to overview the potential imaging markers for individual diagnosis, prognosis, and treatment response prediction in malignant glioma. Furthermore, the correlation between imaging findings and biological and clinical information of glioma patients is reviewed. **Materials and Methods:** The search strategy in this study is to select related studies from scientific websites such as PubMed, Scopus, Google Scholar, and Web of Science published until 2022. It comprised a combination of keywords such as Biomarkers, Diagnosis, Prognosis, Imaging techniques, and malignant glioma, according to Medical Subject Headings. **Results:** Some imaging parameters that are effective in glioma management include: ADC, FA, K^{trans}, regional cerebral blood volume (rCBV), cerebral blood flow (CBF), v_e, Cho/NAA and lactate/lipid ratios, intratumoral uptake of ^{18}F-FET (for diagnostic application), RD, ADC, v_e, v_p, K^{trans}, CBF_{T1}, rCBV, tumor blood flow, Cho/NAA, lactate/lipid, MI/Cho, uptakes of ^{18}F-FET, ^{11}C-MET, and ^{18}F-FLT (for prognostic and predictive application). Cerebral blood volume and K^{trans} are related to molecular markers such as vascular endothelial growth factor (VEGF). Preoperative ADC_{min} value of GBM tumors is associated with O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status. 2-hydroxyglutarate metabolite and dynamic ^{18}F-FDOPA positron emission tomography uptake are related to isocitrate dehydrogenase (IDH) mutations. **Conclusion:** Parameters including ADC, RD, FA, rCBV, K^{trans}, v_p, and uptake of ^{18}F-FET are useful for diagnosis, prognosis, and treatment response prediction in glioma. A significant correlation between molecular markers such as VEGF, MGMT, and IDH mutations with some diffusion and perfusion imaging parameters has been identified.

Keywords: *Biomarkers, diagnosis, imaging techniques, malignant glioma, prognosis*

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Introduction

A glioma is a primary central nervous system malignancy in adults with poor prognosis.[1,2] Grades 1 and 2 are known as low-grade glioma (LGG), and grades 3 and 4 are known as high-grade glioma (HGG). Standard management of malignant glioma usually is surgery followed by concomitant and adjuvant chemotherapy with temozolomide (DNA alkylating agent).[3] The limitations in developing treatment management for glioblastoma include the presence of blood–brain barrier,[4] high resistance to radiation,[5] and abnormality of blood vessels which cause an undesirable and hypoxic microenvironment, thereby increasing radiation resistance and disrupting chemotherapy. Glioblastoma also comprises distinct cancer cells including stem cells, initiating cells, and propagating cells which are extremely resistant to typical chemo- and radiation therapy and can make severe tumor recurrence.[6]

GBM tumors suffer from inter- and intratumor heterogeneity.[4] Intratumor heterogeneity challenges tumor identification and progression of impressive and efficient treatments.[4]

Furthermore, early treatment evaluation is also tough for glioma patients. After completion of RT, the nontumoral increment in contrast-enhancing lesion extent or pseudoprogression occurs in high-grade brain tumor patients.[7] To discriminate between pseudoprogression and early progression of the disease by

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conventional methods, patients should be followed for an extended time or alternative imaging techniques should be applied.[1] Quantitative evaluation of functional and metabolic alterations in tumor can be obtained using advanced imaging techniques including perfusion-weighted imaging, proton magnetic resonance spectroscopy (1H-MRS), and positron emission tomography (PET).[8] Using a biomarker, the effectiveness of a treatment protocol and its potential complications for each patient may be assessed. The purpose of this article is to overview the potential imaging markers for individual diagnosis, prognosis, and treatment response prediction in malignant glioma patients and correlation between imaging findings and biological and clinical information of glioma patients. The remainder of this article is organized as follows. After materials and methods section, imaging role in clinical management of glioma including diagnosis, prognosis, and treatment response prediction is given in sections "Diagnostic Imaging Techniques" and "Prognostic and Predictive information." The advantages and disadvantages of the imaging modalities are summarized in Table 1. Next, in section "Correlation between Imaging Findings and Biological and Clinical Information of Glioma," a brief overview of the correlation between imaging findings and biological and clinical information of glioma is presented.

Materials and Methods

The search strategy conducted in this study was to select relevant studies from scientific websites such as PubMed, Scopus, Google Scholar, and Web of Science published until 2022. It comprised a combination of main keywords such as Biomarkers, Diagnosis, Prognosis, Imaging techniques, and malignant glioma which were selected according to Medical Subject Headings.

The inclusion and exclusion criteria in this study were as follows: studies including books, reviews, and original articles investigated the use of imaging markers for diagnosis, prognosis, and treatment response prediction in glioma, as well as studies examined the relationship between these markers and biological markers were included in the study. The use of articles in the languages other than English, abstracts presented in the conferences, articles before final publication, letters, reports, technical reports, and articles related to other brain cancers were considered as the exclusion criteria. Table 2 summarizes some studies about the application of different medical imaging modalities in diagnosis, prognosis, and treatment response prediction of glioma.

Results

Diagnostic imaging techniques

Computed tomography

Computed tomography (CT) scan has been the main method of imaging for treatment planning in radiation oncology. However, in brain tissue, where most solid tumors and adjacent organs at risk (OARs) have similar electron densities, insufficient contrast in CT images can confuse the determination of target and OARs.[48] Therefore, it is necessary to use other imaging modalities and techniques as a complement to CT scan for its defects.[49]

Table 1: Imaging modalities and techniques used in diagnosis, prognosis, and treatment response prediction associated with glioma with some of their advantages and disadvantages

Imaging modality	Diffusion MRI	Perfusion MRI			MRS	PET
		DSC	DCE	ASL		
Advantages	Widespread availability, fast acquisition time without specialized hardware, detection of some pathological changes in its early stages[9]	Short acquisition time, easy analysis, high temporal resolution[10,11]	Higher spatial resolution than DSC, absolute measurements of plasma volume and K^{trans}[11,12]	Noninvasive[13]	Noninvasive, 3D evaluation of tumor heterogeneity (research application)[14]	Reproducibility due to the low half-life of radiotracers, accurate quantitative measurements[12]
Disadvantages	Low image quality (low SNR, limited spatial resolution, distortion, artifacts), overlap between ADCs of grade II astrocytomas and glioblastomas[9,15]	Indirect detection of the injected contrast material, susceptibility artifacts[11,12]	Indirect detection of the injected contrast material, needing high temporal resolution, needing an appropriate analysis model, not suitable for glioma with BBB disruption or vessel leakage[16,17]	Poor labeling efficiency, low SNR, high sensitivity to patient movement, needing standardization methods[12,18]	Technical problems such as differences in: acquisition techniques, calculation of metabolites ratio, and in volume averaging. limited spatial resolution, low SNR[19,20]	High costs of imaging, impossibility of using PET imaging in clinical emergencies, lack of anatomic information[12,21]

DSC – Dynamic susceptibility contrast; DCE – Dynamic contrast-enhanced; ASL – Arterial spin labeling; MRI – Magnetic resonance imaging; MRS – Magnetic resonance spectroscopy, PET – Positron emission tomography; BBB – Blood–brain barrier; SNR – Signal-to-noise ratio; ADCs – Apparent diffusion coefficients; 3D – Three-dimensional

Table 2: Some imaging modalities and techniques and their assessed parameters used in diagnosis, prognosis, and treatment response prediction of glioma

Application	Modality	Imaging techniques	Assessed parameters	Reference
Diagnostic	Diffusion MRI	DWI	ADC	[22-24]
	Perfusion MRI	DCE	CBV, K^{trans}, v_e	[25-27]
	Perfusion MRI	ASL	CBF	[18,28]
	Perfusion MRI	DSC	CBV, rCBV	[10,18,26-28]
	MRS		Cho/NAA and lactate/lipid levels	[19,29]
	PET		Intratumoral uptake of ^{18}F-FET	[30,31]
Prognostic and treatment response prediction	Diffusion MRI		RD, ADC value, and longitudinal DTI	[32-34]
	Perfusion MRI	DCE	K^{trans}, v_p, v_e, CBF_{T1}	[35-37]
	Perfusion MRI	DSC	rCBV, CBF, EF	[38,39]
	Perfusion MRI	ASL	TBF	[40]
	MRS		Cho/NAA, lactate/lipids, and MI/Cho ratios	[41,42]
	PET		Intratumoral uptake of ^{18}F-FET, reduced uptake of ^{11}C-MET, ^{18}FET, and ^{18}F-FLT	[43-47]

MRI – Magnetic resonance imaging; MRS – Magnetic resonance spectroscopy, PET – Positron emission tomography; DWI – Diffusion-weighted imaging; DCE – Dynamic contrast-enhanced; ASL – Arterial spin labeling; DSC – Dynamic susceptibility contrast; MI – Myo-inositol; TBF – Tumor blood flow; CBF – Cerebral blood flow; CBV – Cerebral blood volume; rCBV – Regional CBV; DTI – Diffusion tensor imaging; ADC – Apparent diffusion coefficient; ^{18}F-FET – ^{18}F-fluor-ethyl-tyrosine; ^{18}F-FLT – ^{18}F-fluorothymidine; ^{11}C-MET – L-[methyl-^{11}C] methionine; NAA – N-acetylaspartate; Cho – Choline; RD – Radial diffusivity; EF – Extraction fraction

Magnetic resonance imaging

Standard sequences of magnetic resonance imaging

Magnetic resonance imaging (MRI) is used as the primary method of early diagnosis in glioma.[4] MRI sequences which are essential for glioma tumor visualization and provide important information before and during the tumor resection are pre- and postcontrast T1-weighted and T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) sequences.[16,50] T1-postcontrast imaging is very useful in detecting HGG.[16] T2-FLAIR is more suitable for visualizing LGG and areas of edema and tumor spread outside the contrast-enhancing areas on T1 sequences for HGG. Despite the advantage of using standard MRI sequences which has been supported by many studies,[16,51-54] their use has some limitations in diagnosis of gliomas. For example, in some cases of GBM, T1-postcontrast images show the absence or lack of enhancement.[16] In addition, T2 and FLAIR sequences are limited in distinguishing LGG from HGG.[16] Therefore, for characterizing glioma tumor more completely, it is necessary to use other imaging sequences and modalities.

Diffusion magnetic resonance imaging

In diffusion-weighted imaging (DWI), the motion of water molecules and ultimately the magnetic resonance signal is affected by microstructural changes. Thus, using diffusion tensor imaging (DTI) to measure diffusion in several directions, the average molecular motion (ADC criterion) and information about the arrangement and integrity of cellular structures (fractional anisotropy [FA]) are also obtained.[2] In terms of application to brain tumors, FA shows the amount of anisotropy in each voxel (anisotropy is high in white matter and low in gray matter)[55] which can be used as a measure for degradation of healthy white matter.[2] Sugahara *et al*. evaluated the cellularity and grading of glioma using DW-MRI with echo-planar imaging technique and demonstrated that the minimum ADC of the tumor increases with increasing tumor grade and cellularity.[56] In diffusion imaging, it is possible to differentiate between the edema and the infiltrative tumor cells, the neoplastic areas from the abscess, and primary central nervous system lymphoma from HGG.[4,22] Furthermore, advanced sequences such as DTI can be utilized to exhibit the transposition of white matter tracts resulting from the existence of tumor.[4] Diffusion kurtosis imaging is an emerging diffusion technique that provides more information about tissue microstructural changes with higher sensitivity and accuracy than DWI and DTI.[57,58]

Perfusion magnetic resonance imaging

In perfusion techniques, blood is followed to the target tissue within the vascular system with or without an injected contrast agent.[12] Then, physiologic and hemodynamic data are measured and their relationship with the tumor biology can be obtained.[59,60] Perfusion imaging techniques that can be used for brain tumors include dynamic susceptibility contrast (DSC)-MRI, dynamic contrast-enhanced (DCE)-MRI, arterial spin labeling (ASL)-MRI, perfusion computed tomography, PET, and single-photon emission computed tomography.[12,61,62] Some of the perfusion parameters include cerebral blood volume (CBV), regional CBV (rCBV), cerebral blood flow (CBF), permeability of blood vessels (K^{trans}), volume

fraction of extravascular extracellular space (v_e), and plasma volume per unit volume of tissue (v_p).[24,60]

Magnetic resonance perfusion imaging techniques including DSC, DCE, and ASL can be used to distinguish between high and low grades of glioma.[10,16,63] Studies have introduced CBV and rCBV as angiogenesis markers to distinguish HGG from LGG.[64-66] In a meta-analysis study by examining the performance of DCE and DSC imaging techniques in the diagnosis of glioma grade, it was concluded that these two techniques and their parameters including K^{trans}, v_e, rCBV, and CBF are reliable in differentiation between high- and low-grade gliomas and rCBV is the best parameter for glioma characterization, preoperatively.[24] K^{trans} is able to distinguish between Grade II, III, and IV gliomas.[26] HGGs have higher K^{trans} than LGGs.[67,68] In addition, CBF parameter obtained from ASL technique is able to distinguish between LGG and HGG, if standardization methods are used in postprocessing algorithms to make the data reliable.[18]

There are more recent MRI techniques that are not widely used clinically and are able to distinguish LGG from HGG, e.g., intravoxel incoherent motion. In this technique, imaging is performed based on the diffusion and perfusion of tissue water molecules without the need to inject exogenous contrast.[69-71]

Magnetic resonance spectroscopy

MRS offers information about biochemical changes in brain tissue by analyzing the concentration of metabolites. MRS can be used to distinguish normal brain tissue from tumor, glioma from noninfiltrative tumor such as metastases, and also to determine tumor grade.[49,72,73]

With increasing glioma grade, the amount of Cho and lipid increases, and in cases of metastasis, the amount of lipid is higher than in HGG cases.[29] MRS proton-detectable metabolites such as Cho and NAA are probable biomarkers for tumor activity. Cho represents the metabolism of cellular membrane turnover function. NAA, as a neuronal density marker, decreases in tumors owing to the lack of neurons. GBM illustrates a growth in the ratio of Cho/NAA.[19,49,74,75] Furthermore, creatine (Cr) is a marker of normal cellular metabolism. Lactate, lipid, and myo-inositol (MI) reflect hypoxia, necrosis, and astrocyte integrity, respectively.[19] It has shown a direct relationship between tumor grading and the ratios of Cho/NAA and Cho/Cr.[76-79] Furthermore, an inverse relationship between the ratio of MI/Cr and tumor grading in cerebral astrocytoma patients has been concluded.[80] Ratios such as Cho/NAA and lactate/lipid levels can be used to diagnose different intracranial tumor types and grades or distinct tumor recurrence from radiation necrosis.[4]

Low signal to noise ratio in MRS causes the decrease in the spatial resolution. Therefore, the assessment of intratumoral heterogeneity is limited.[20] Chemical exchange saturation transfer is another MRI technique that detects metabolites with a higher spatial resolution than MRS and can be used to investigate intratumoral heterogeneity in glioma.[81]

Positron emission tomography

PET is another imaging modality widely used for imaging of gliomas using their molecular and biochemical attributes such as glucose, nucleoside, or amino acid metabolism.[8] The use of PET imaging for the first time in oncology dates back to the early 1980s, when 2-deoxy-2 [^{18}F] fluoro-D-glucose (FDG), ^{11}C-labeled amino acids, and nitrosourea analogs were used for brain tumors.[82-84] Since the late 1970s, the clinical use of alternatives to FDG-PET, like radiolabeled amino acids, has been propounded for cancer imaging.[8] Tracers including ^{11}C-MET and ^{18}FET are more useful than ^{18}F-FDG and are most widely used.[49] ^{11}C-MET and ^{18}FET are preferable for diagnosis of glioma in areas of infiltrating tumor cells that are not visualized by MRI.[4] It has been shown that using ^{18}FET data for RT planning compared to conventional methods increases the treatment volumes.[85,86] In clinical trials, nucleic acid tracers like ^{18}F-FLT have been shown to be better than ^{18}F-FDG in differentiation between LGG and HGG.[4] The relation between nucleic acid tracers and histological proliferation markers has been well documented.[87] The most common PET radiotracers for use in brain imaging are amino acid PET radiotracers including MET, FET, ^{18}F-fluoro-l-dihydroxy-phenylalanine (FDOPA), and AMT.[8]

Prognostic and predictive information

Magnetic resonance diffusion and perfusion imaging

Predicting the true progression of the tumor can be achieved using diffusion and perfusion parameters such as ADC and rCBV,[88,89] k^{trans} and v_e values,[90] extraction fraction (EF),[39] and FA from longitudinal DTI.[33] In diffusion imaging, longitudinal variations in water molecules' mobility as an early indicator of treatment response are also correlated with overall progression and survival time.[4] The correlation between pretreatment DWI-MRI parameters, ADC and diffusion index (RD), of brain tumor patients and response to RT has been indicated.[34] Minimum ADC value before surgery has a negative association with the Ki-67 labeling index and can be applied to predict progression in malignant astrocytic tumors, including GBM and anaplastic astrocytoma.[91] Hamstra *et al*. showed that functional diffusion map data have potential to be used as an early predictor of treatment response and overall survival (OS) in HGG.[92]

The most important prognostic molecular factors in gliomas are isocitrate dehydrogenase (IDH) mutations, which can be detected using DSC-CBV and DSC-CBF parameters. DCE permeability parameters, including K^{trans}, v_p, and v_e, have also shown a decrease in the case of IDH mutant gliomas compared to IDH-wild-type.[35,36,38] On

the other hand, the results of studies on the usefulness of ASL-CBF in distinguishing these two types of gliomas are not consistent.[38,93,94] The study by Yamashita *et al*. demonstrated that combination of tumor blood flow obtained from ASL and measurement of necrotic area from routine MRI is a surrogate marker for predicting the IDH1 status in GBM patients.[40] In addition, Nguyen *et al*. showed that DCE modeling can be used to predict OS in patients with glioma.[95] In a study carried out by Larsson *et al*., the prognostic value of DCE parameters including K^{trans} and CBF_{T1} in early prediction of OS was more promising than DSC parameters.[96]

Magnetic resonance spectroscopy

Kumon *et al*. concluded a direct relationship between the ratio of MI/Cho and better prognosis of IDH-wild-type (IDH-wild-type) GBM patients in preoperative MRS analysis.[42] In another study, after investigation of the recurrence free survival (RFS) and MRS parameters including NAA/Cr, Cho/Cr, Cho/NAA, and MI/Cr ratios in HGG patients, the authors concluded that the Cho/ Cr ratio has a significant correlation with RFS.[97]

Positron emission tomography

Valuable prognostic and predictive information is obtained using some PET tracers. For example, ^{18}F-FLT was introduced as a predictor of response to bevacizumab treatment in glioblastoma patients, which performed better than MRI in predicting early and late response to treatment and OS.[46] MET-PET has also been proposed as a predictor of treatment response in malignant glioma.[45,98] In a prospective phase II study, after using postoperative ^{18}FET-PET for definition of CTV in treatment planning, Piroth *et al*. concluded that postoperative tumor volume in ^{18}FET-PET has a significant relationship with progression-free survival and OS in GBM patients.[99] It is also possible to monitor tumor oxygen deficiency, which is a substantial characteristic of HGGs, using PET imaging.[4]

All imaging modalities and techniques have certain advantages and disadvantages which some of them are given in Table 1. The physicians can choose the best option based on the available facilities and the patient's condition.

Correlation between Imaging Findings and Biological and Clinical Information of Glioma

Vascular permeability, the presence of vascular endothelial growth factor (VEGF)/VPF, and angiogenesis are important mediators of tumor growth that can be obtained by perfusion and permeability imaging.[100,101] The amount of vascular proliferation is an important criterion in the histopathological description of tumor biology and prognosis.[60] CBV measurements have a strong and direct relationship with histopathological grade of cerebral gliomas and may be employed to assess the effect of treatment or to distinguish between tumor recurrence and the posttreatment radiation effect.[60,102-104] Mathematical modeling by DCE imaging has shown that K^{trans} is associated with tumor aggressiveness.[95] CBV and K^{trans} have a direct relationship with molecular markers such as VEGF.[60,105]

There are also imaging markers related to the O6-methylguanine-DNA methyltransferase (MGMT) status; for example, preoperative minimum ADC value of GBM tumors is associated with MGMT promoter methylation status.[106] Furthermore, K^{trans} has potential to be used as an imaging marker because of its significantly higher value in the MGMT-methylated group of GBM patients.[107] Another study has suggested the use of radiomic features extracted from pretreatment ^{18}FDOPA-PET images to predict the MGMT status in glioblastoma patients.[108]

MRS can noninvasively detect IDH mutations using the levels of the metabolite 2-hydroxyglutarate (2HG), so that in IDH-mutant tumors, the amount of 2HG metabolite increases, and in the IDH-wild-type, its amount is normal.[7] 2HG is an oncometabolite that affects the hypoxia-inducible factor-1α, which is a tumor progression factor in GBM.[109] It should be noted that accurate diagnosis using MRS has many advantages over biopsy, including low risk, reproducibility, and the possibility of noninvasive examination of different parts of the tumor, but under the appropriate acquisition and quantification techniques to prevent false results.[109] Using dynamic ^{18}F-FDOPA PET uptake parameters, the presence of IDH mutation in newly diagnosed gliomas can be predicted.[110] Furthermore, via radiomic analysis of ^{18}F-FDG PET images, the IDH genotype status was effectively and noninvasively predicted in glioma patients.[111]

Conclusion

Along with challenges involved in development of an effective treatment and early treatment evaluation of glioma, the identification of specific and noninvasive biomarkers will be useful. Prognostic information and predicting individual patient's response to the treatment can be obtained using specific biomarkers. Substantial data on cell proliferation, angiogenesis, hypoxia, and metabolic activity using advanced imaging techniques are provided for better management of glioma. For example, in diffusion imaging, it is possible to distinguish the edema from the infiltrative tumor cells and the neoplastic areas from the abscess. ADC and RD can be related to treatment response in pretreatment DW images of tumor. Tumor physiological parameters obtained in perfusion MRI techniques such as CBV, rCBV, CBF, K^{trans}, and v_p can be correlated with tumor biology. Using appropriate acquisition and quantification techniques to prevent false results, MRS can discriminate between normal tissue and tumor, identify types and grade of tumor, predict survival, or differentiate between tumor recurrence and radiation necrosis. Ratios of

Cho/NAA, Cho/Cr, and MI/Cr have diagnostic information, and Cho/Cr ratio has a significant correlation with RFS. The use of PET as a complementary modality to MRI in the clinical management of brain tumors, including glioma, is increasing because of its accuracy in quantitative measurements. The most common amino acid PET tracers for use in brain cancer including glioma are ^{11}C-MET, ^{18}FET, FDOPA, and AMT.

Vascular proliferation is an important factor in describing tumor biology and prognosis. For this reason, rCBV is related to tumor grade and histopathology results. K^{trans} is also related to tumor aggressiveness. Moreover, both K^{trans} and CBV have a direct relationship with the molecular markers such as VEGF. Minimum ADC values of GBM tumors are related to MGMT status. IDH mutations can be detected using 2HG MRS metabolite and dynamic ^{18}F-FDOPA PET uptake parameters.

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Conflicts of interest

There are no conflicts of interest.

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