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SYSTEMATIC REVIEW

Quantitative magnetic resonance imaging and radiogenomic biomarkers for glioma characterisation: a systematic review

[1,2]POHCHOO SEOW, MSc, [1,2]JEANNIE HSIU DING WONG, PhD, [3]AZLINA AHMAD-ANNUAR, PhD, [4]ABHISHEK MAHAJAN, MBBS, MD, [5]NOR ANIZA ABDULLAH, PhD and [1,2]NORLISAH RAMLI, FRCR

[1]Department of Biomedical Imaging, University of Malaya, Kuala Lumpur, Malaysia
[2]Department of Biomedical Imaging, University of Malaya Research Imaging Centre, University of Malaya, Kuala Lumpur, Malaysia
[3]Department of Biomedical Science, University of Malaya, Kuala Lumpur, Malaysia
[4]Department of Radiodiagnosis and Imaging, Tata Memorial Hospital, Mumbai, India
[5]Department of Computer System and Technology, University of Malaya, Kuala Lumpur, Malaysia

Address correspondence to: Prof Norlisah Ramli
E-mail: *norlisahramli@gmail.com*

Objective: The diversity of tumour characteristics among glioma patients, even within same tumour grade, is a big challenge for disease outcome prediction. A possible approach for improved radiological imaging could come from combining information obtained at the molecular level. This review assembles recent evidence highlighting the value of using radiogenomic biomarkers to infer the underlying biology of gliomas and its correlation with imaging features.

Methods: A literature search was done for articles published between 2002 and 2017 on Medline electronic databases. Of 249 titles identified, 38 fulfilled the inclusion criteria, with 14 articles related to quantifiable imaging parameters (heterogeneity, vascularity, diffusion, cell density, infiltrations, perfusion, and metabolite changes) and 24 articles relevant to molecular biomarkers linked to imaging.

Results: Genes found to correlate with various imaging phenotypes were *EGFR, MGMT, IDH1, VEGF, PDGF, TP53,* and *Ki-67*. *EGFR* is the most studied gene related to imaging characteristics in the studies reviewed (41.7%), followed by *MGMT* (20.8%) and *IDH1* (16.7%). A summary of the relationship amongst glioma morphology, gene expressions, imaging characteristics, prognosis and therapeutic response are presented.

Conclusion: The use of radiogenomics can provide insights to understanding tumour biology and the underlying molecular pathways. Certain MRI characteristics that show strong correlations with *EGFR, MGMT* and *IDH1* could be used as imaging biomarkers. Knowing the pathways involved in tumour progression and their associated imaging patterns may assist in diagnosis, prognosis and treatment management, while facilitating personalised medicine.

Advances in knowledge: Radiogenomics can offer clinicians better insight into diagnosis, prognosis, and prediction of therapeutic responses of glioma.

INTRODUCTION

Gliomas, which comprise 27% of all brain tumours, are lethal primary malignant brain tumours originating from the interstitial tissue of the brain.[1] Gliomas are categorised as diffuse astrocytic and oligodendroglial tumours, other astrocytic tumours, ependymal cell types and neuronal and mixed neuronal-glial tumours according to the World Health Organization (WHO) guidelines. A recent upgrade of the WHO guidelines feature integrated molecular parameters into histology that underlines the importance of radiogenomics in the classification of tumour entities.[2,3] The severity of the grade depends on tumour growth, localized invasion, cell pleomorphism, mitotic activity, vascular proliferation, necrosis, and resistance to therapy.

To date, MRI is the modality of choice as it offers valuable information on overall tumour structure, composition, physiology and function.[4] Tumour characteristics examined such as intensity distribution, enhancement, size, shape, structure, location, volume, border, focality, subventricular zone involvement, cystic changes, the percentage of necrosis and tumour volume are often inadequate for clinical use because of the irregular shape and heterogeneous composition of the tumours.[5–9] Histopathological grading serves as the gold-standard but suffers from several drawbacks such as intra- and interobserver variability, sampling error, tumour heterogeneities, and risk of surgical complications in patients.[10] Quantitative imaging biomarkers derived from advanced MRI techniques, namely diffusion-weighted imaging, perfusion-weighted imaging, diffusion tensor imaging, diffusion kurtosis imaging and magnetic resonance spectroscopy are used to define tumour morphology and functionality.[4,11,12]

Glioma detection and grading at its earliest stage is crucial for early intervention to improve prognosis and minimise neurocognitive risks. The problem of grading glioma accurately is not trivial. High diversity of tumour properties, even within a single tumour, is a big challenge to determine the grades and subtypes. The heterogeneous nature of the tumours further complicates histopathological observations and this can affect treatment decisions and management. To cap the complexity of the disease, different responses to treatments among patients are often seen due to the differences in the genetic profiles of the tumours.[13,14] Hence, the use of radiogenomic biomarkers may provide a holistic approach for the treatment of glioma.

Radiogenomics is an evolving new field that studies the link between gene expression patterns and imaging phenotypes for diagnosis, prognosis, and prediction of therapeutic responses in cancer.[15,16] The underlying inter- and intratumoral gene expression patterns that steer the unique characteristics and morphological manifestation of glioma can be captured by quantitative imaging.[5,9,15–19] Radiogenomics holds the potential for targeted therapies, whereby therapeutic treatments are tailored to the individual tumour's genetic profile based on indications from imaging features. There is a need to identify biomarkers that can reflect genetic profiles to better characterise the tumours, so that clinicians can make better decisions when administering treatment.

While there have been a number of studies looking at this aspect in glioma grading, it is still unclear which genes or pathways offer the most comprehensive personalised approach in practice.[20,21] This paper aims to provide a systematic review of these recent studies specifically looking at the use of MRI biomarkers in characterising glioma. We plan to stratify radiophenotypes that could serve as molecular surrogates to infer specific gene expression patterns from the review.

METHODS AND MATERIALS

Eligibility criteria and search strategy

We performed a systematic review of imaging biomarkers (radiogenomics) of glioma literature according to the PRISMA (Preferred Reporting Items for Systemic Review and Meta-Analyses) guidelines.[22,23] Our review comprised of a detailed set of research questions and a search strategy that included screening criteria for titles and abstracts, followed by the selection of full-text articles. The detailed research questions were established using the patient, intervention, comparator, outcome and study design approach. The questions were devised as follows: what are the key genes associated with imaging characteristics of gliomas? What are the changes in gene expression of the tumours? Are gene expression patterns linked to specific MR imaging features? What are the correlations between the radiogenomic biomarkers associated with the tumours and the phenotypes reflected by MRI?

The inclusion criteria for full-text article assessment were randomised or cohort MRI studies of glioma patients. The exclusion criteria were studies on paediatric populations, radiotherapy or chemotherapy studies and drug studies such as clinical trials, animal experiments, biopsies or histopathological studies, cell culture, and toxicity tests. Pubmed and Google Scholar were used to search the Medline database. The keywords used in Medline included "glioma", "magnetic resonance imaging", "MRI", "biomarkers" and "glioblastoma multiforme". Full-article assessments were conducted to determine the compliance of the studies with the inclusion and exclusion criteria. The searches were done by PS and reviewed by NR, JHDW, and AAA respectively.

Study selection and data extraction

Only studies published in English after 2002 were selected and the last search was on 30 October 2017. Relevant data regarding imaging features and molecular profiles were extracted from each article. The data collected were categorised into gene groups, associated with different imaging characteristics of tumour.

RESULTS

Study selection

The literature search and study selection showed 59 records were included in the final stage of the literature review where 38 full text articles investigated on quantifiable biomarkers (Figure 1). From the records, 14 articles were related to quantifiable imaging parameters (Table 1) while 24 articles investigated the relations between imaging biomarkers and genetic profiles (Table 2). There were overlaps in both of the tables as some of the studies investigated several parameters. The main findings of the studies were also recorded (Supplementary Material 1) while the PRISMA checklist was provided as Supplementary Material 2.

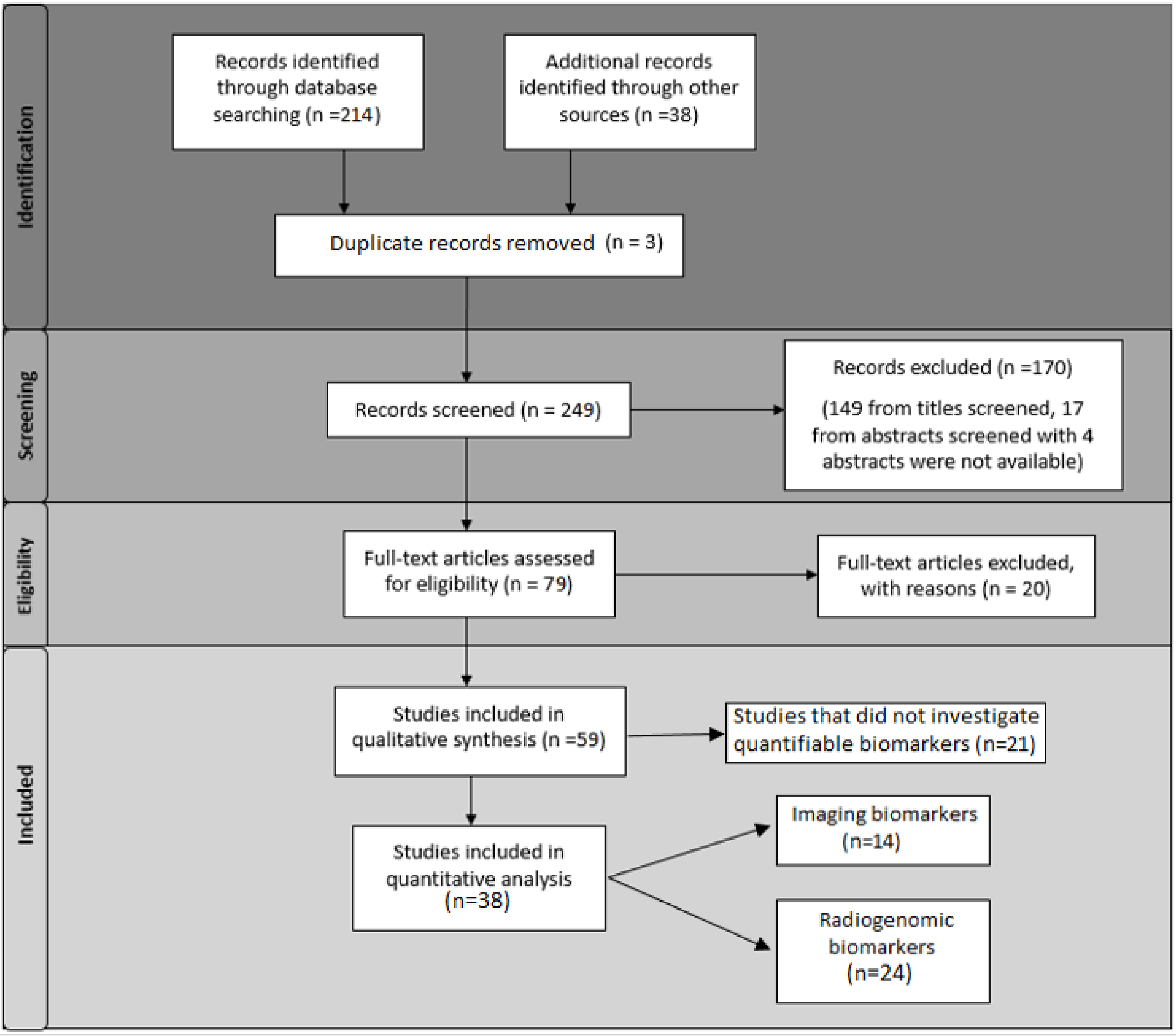
Findings

Table 1 lists the quantitative MRI biomarkers that are reported in the literature reviewed. Figures 2–6 show the structural and functional images of different glioma grades acquired from conventional and advanced MRI techniques, in relation to gene expression. We list the gene expression profiles linked to glioma characteristics in Table 2.

The key genes

The gene expression profiles found to be associated with the imaging features are listed in the following sections. The order of the gene expression profiles discussed is according to numbers of studies done, rather than their interpretive significance. Figure 7 is a schematic diagram to summarise the relationship between glioma morphology, imaging features, and gene expression profiles, which can be inferred from MRI techniques. From the figure, a complex pattern of involvement is evident as a single gene may have roles in different tumour characteristics,

Figure 1. Literature assessment. Flow diagram of literature assessment.



meanwhile, a single tumour characteristic could be due to many different genes.

Epidermal growth factor/receptor (EGFR)

EGFR is the receptor for epidermal growth factor, and amplification/overexpression of the *EGFR* locus is found in about 42% of primary glioblastoma multiformes (GBM).[35] *EGFR* amplification in histologically pure anaplastic oligodendroglioma (ODG) is indicative of GBM. *EFGR* overexpression indicated poor outcome and correlated with decreased overall survival in GBM.[7,55] The stratification of GBM into four distinct molecular subtypes (classic, mesenchymal, neural and proneural) are differed by distinct prognoses and responses to therapy based on gene expression.[56] The classic subtype has a strong association with astrocytic signature with *EGFR* amplification.

EGFR was identified as a significant glioma biomarker in 41.7% of the studies reviewed. The pathway activation of *EGFR* is associated with increased motility, invasion, angiogenesis, tumour cell proliferation, reprogramming of tumour metabolism, and inhibition of apoptosis.[36,37,57]

Contrast enhancement of the solid region of tumour in T_1W (T_1 weighted) is often related to the aggressiveness of lesions,[4,6,9] however, many low-grade gliomas show enhancement and one-third of non-enhancing gliomas are malignant.[6] The solid region of the tumour and its surrounding tissues are comprised of actively proliferating cells such as invasive tumour cells, microglial cells and reactive astrocytes.[31] In terms of enhancement, *EGFR* amplification/overexpression was associated with higher T_1 +C (post-contrast) and T_2/FLAIR hyperintense volume, higher ratio

Table 1. Quantitative MRI biomarkers mentioned in the studies

Characteristics	Imaging biomarkers[a]	Techniques	Number of studies	Ref
Heterogeneity	Enhancement and necrosis	MRI	1	4
Vascularity	Uncorrected CBV ratio and FPS ratio	MRI + PWI (DSC / DCE)	6	24
	Min and max relative CBV and relative CBF			11,25,26
	K_{trans} and V_e			27
	Peak height in ET & non-ET			28
Non-Gaussian diffusion/Cell density/ cellularity	ADC, slow diffusion coefficient (D_{slow}), DDC and heterogeneity index (α)	MRI + DWI/IVIM	3	4,29,30
Infiltrations along WM tracts/ micro-vascularity	FA, MD, and tensor decomposition p & q maps & fDM	MRI + DTI	6	26,31,32
	Relative anisotropy and radial diffusivity			33
	Diffusion trace in ET			28
Metabolite changes	Lip/tCho	MRI + MRS	3	11
	Cho/Cr, MI/Cr, Lac/Cr, NAA/Cr			31
	Lipid quantification: Signal loss ratio in solid and cystic subregions	MRI + MRS+IOP		34
Kurtosis	Mean kurtosis	DKI	1	11

ADC, apparent diffusion co-efficient; CBF, cerebral bloodflow; CBV, cerebral blood volume; Cho, choline; Cr, creatine; DDC, distributed diffusion coefficient; DWI, diffusion-weighted imaging; DTI, diffusion tensor imaging; ET, enhancing tumour; IVIM, intravoxel incoherent motion; FA, fractional anisotropy; fDM, functional diffusion map; FPS, first pass slope; K_{trans}, volume transfer constant; IOP, in and opposed-MRI; Lip, lipid; MD, mean diffusivity; MI, myo-inositol; Lac, lactate; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; PWI, perfusion-weighted imaging; V_e, volume of extravascular extracellular space per unit volume of tissue; WM, white matter.

MRI refers to structural MRI [T_1-weighted, T_2-weighted and Fluid Attenuation Inversion Recovery (FLAIR) sequences].

[a] only biomarkers that are statistically significant ($p < 0.05$) are reported.

of the contrast enhancing volume to the necrotic tumour volume and greater ratio of T_2-bright volume to T_1-enhancing volume (including internal necrosis) in GBM[35,36,38,39,51,58] (Figure 2). *EGFR* amplification/ overexpression/ mutation is related to angiogenesis, with a resultant increase in cerebral blood volume (CBV), cerebral blood flow (CBF), plasma volume and contrast transfer coefficient in MR perfusion.[36,40,41] Metabolite changes such as reduced N-acetyl-aspartate (NAA) levels, lower creatine (Cr) and lower myoinositol (MI) in high-grade gliomas (HGG) and increased lactate proportionally with volumes of necrosis lesion,[11,31,49,59–62] and restricted water diffusion[36,37] are also related to *EGFR* amplification/ overexpression/ mutation.

O6-methylguanine-DNA-methyltransferase (MGMT)

The second gene that appears most frequently in the studies reviewed (20.8%) is the *MGMT* gene and has been reported for 30–60% in GBM. The *MGMT* gene encodes a DNA repair protein that is involved in cellular defense against mutagenesis and toxicity from alkylating agents.[43] GBM with *MGMT* promoter methylation demonstrated more favourable prognosis in terms of longer median survival.[6,48,51,63,64] GBM with *MGMT* promoter methylation showed better treatment response[6,51] due to decreased *MGMT* protein expression that reduces DNA repair activity against temozolomide, a DNA alkylating agent. Thus, the sensitivity to therapy improves due to the increase in endothelial permeability that facilitates the penetration of drugs and their delivery.[43,63]

Hypermethylated *MGMT* tumours tend to have mixed-nodular enhancement, non-temporal lobe lesions, and often show radiation or treatment-induced pseudo-progression.[44] On the contrary, unmethylated *MGMT* tumours have high occurrences of temporal lobe lesions, ring enhancement, and true progression[35] (Figure 3). Tumour characteristics such as cellular density, treatment response, and texture features are linked to *MGMT* methylation status.[9,43,45,53,59] Increased apparent diffusion coefficient (ADC) values derived from DWI implicate changes in tumoral water diffusion incited by necrosis or apoptosis,[49] and a higher degree of spatial heterogeneity has been observed in contrast-enhancing unmethylated *MGMT* tumours.[4,9,29] Treatment responses were apparent in infiltrative low-grade gliomas (LGG) as reflected by changes in DTI metrics such as pure isotropic components of diffusion (p) and mean diffusivity (MD) at the tumour borders.[32]

Isocitrate dehydrogenase 1 (IDH1)

IDH1 encodes a metabolic enzyme known as IDH1, which catalyses the conversion of isocitrate to alpha-ketoglutarate. Mutations in *IDH1* are frequently seen in diffuse LGG and secondary GBM.[3,61–64] *IDH1* mutations are also one of the genetic features related to the proneural subtype of GBM[51] that carry better clinical prognosis in terms of overall survival and progression-free survival,[48] and bear favourable overall survival in diffuse astrocytomas and anaplastic astrocytoma.[3,61]

Table 2. The radiogenomic biomarkers linking imaging features/phenotypes to gene expression patterns in the studies

Genes/Molecular biomarkers	Characteristics	Imaging biomarkers	Number of studies	Ref
EGFR	Diffusion	relative CBV, PSR	10	13
	Morphology	Anatomic location (radiogenomic maps)		35,36
		Percentage of CE, NE, necrosis & oedema and largest diameter on lesion		7
	Morphology, diffusion & interaction with ECM	Border sharpness, restricted water diffusion, ADC		37
	Gene expressions	CE, necrosis, mass effect, oedema, cortical involvement, CE:N volume ratio, *T2* heterogeneity		38
		Infiltration, proliferation, neurogenesis and synaptic transmission		39
	Perfusion	VP & K_{trans}		40
		Normalized CBV & CBF		41
		Mean & relative TBF		42
MGMT methylation status	Perfusion	K_{trans}	5	43
		Normalized CBV		44
	Morphology	Anatomic location		35,36]
	Textures	Correlation, energy, entropy & local intensity		45
IDH1	Morphology	Location	4	35
	Metabolite changes	Percentage of CE, NE, necrosis & oedema and largest diameter on lesion 2-hydroxyglutarate (2HG)		7 [46,47
	Perfusion	TBF		48
TP53	Morphology	Percentage of CE, NE, necrosis & oedema and largest diameter on lesion	2	7
	Gene expressions	CE, necrosis, mass effect, oedema, cortical involvement, CE:N volume ratio, *T2* heterogeneity		38
PTEN loss	Morphology	Anatomic location	2	36
		Percentage of CE, NE, necrosis & oedema and largest diameter on lesion		7
Ki-67 index	Diffusion, perfusion, metabolite change & genomics	relative CBF, FA, ADC, Cho/Cr, NAA/Cho, NAA/Cr, Lac/Cr & MI	3	49,50
	Gene expressions	CE, necrosis, mass effect, oedema, cortical involvement, CE:N volume ratio, *T2* heterogeneity		38
VEGFR	Morphology and textural	Shape, texture, edge sharpness of necrotic core and surrounding CE rim	2	51
	Vascularization	CBV		52
1p/19q codeletions	Vascularization	relative CBV	1	53
GAP4 and WWTR1 genes	Intensities (ROI), sharpness of lesion boundaries, boundary shapes	Edge sharpness of necrotic portion	1	18

(Continued)

Table 2. (Continued)

Genes/Molecular biomarkers	Characteristics	Imaging biomarkers	Number of studies	Ref
HRAS copy number variation	Contrast enhancement and genetic expressions	Proportion of enhancing tumour & *T1*/FLAIR ratio	1	8
Periostin and miR-219	Cellular invasion	Edema/invasion FLAIR volumes	1	54
Molecular subclasses of GBM	Hemodynamics	relative CBV	1	52

ADC, apparent diffusion coefficient; CBF, cerebral blood flow;CBV, cerebral blood volume; CE, contrast enhancement; CE:*N*, contrast-enhancing volume to the necrotic tumour volume ratio; ECM, extra cellular matrix; *EGFR, epidermal growth factor receptor;* Cho, choline; Cr, creatine; FA, fractional anisotropy; *IDH1, isocitrate dehydrogenase1; Ki-67antigen*; K_{trans}, volume transfer constant; Lac, lactate; *MGMT, O_6-methylguanine-DNA-methyltransferase*; MI, myo-inositol; NAA, N-acetyl aspartate; NE, non-enhanced; *PDGFA, platelet-derived growth factor*; ROI, region of interest; PSR, percent signal recovery; *PTEN, phosphatase and tensin homolog*; TBF, tumour blood flow; *TP53, tumour protein p53*; *VEGFR, vascular endothelial growth factor receptor*; VP, plasma volume.

GBM with *IDH1* mutations tend to be in the left frontal lobe, larger at diagnosis, may be multifocal, have a high prevalence of non-enhancing tumours, cystic and diffuse components, greater frequency of contact with brain ventricles with less necrosis detection and extent of oedema, less frequent vascular abnormalities, increased oligodendroglial morphology and also metabolite changes[35,46,60,64] (Figure 4). Glioblastomas without *IDH1* mutations showed larger volumes of contrast enhancement seen in T_1W + C.[21,35] The conversion to alpha-ketoglutarate by *IDH1* gene is observable using MRS as the elevation of 2-hydroxyglutarate (2HG) co-detected at 2.25ppm and 4.02 ppm that reflect changes in tumour cellularity.[46,47]

1p/19q codeletion status

The combined loss of 1p and 19q chromosome arms is uncommon in glioma and is considered the earliest genetic hallmark of ODG, whereby it is seen in 50–70% of the neoplasms.[65] [20] The complete loss of both chromosomes is associated with good prognosis, longer progression-free survival and increased sensitivity to chemotherapy in ODG and oligoastrocytoma.[66,67]

In conventional MRI studies, ODG with 1p/19q loss is more likely to have indistinct borders on T_1W images, mixed-signal intensities on T_1W and T_2W, paramagnetic susceptibility effect, calcification and infiltrative growth patterns[65,68] (Figure 5). Elevated relative CBV with 1p/19q codeletions suggested increased neovascularity in glioma with oligodendroglial components.[67] The increased ADC values in ODG and 1p/19q codeleted mixed oligoastrocytomas (OA) were associated with the fraction of the tumour cells (relative number of tumour cells per total cells) and degree of axonal disruption in tumour subregions.[66]

TP53

TP53 is a tumour suppressor gene, which encodes a tumour suppressor protein that responds to cellular stresses by inducing cell cycle arrest, apoptosis, senescence, DNA repair or metabolism

Figure 2. A case of grade IV GBM with *EGFR* amplification/overexpression. MRI features showing greater ratio of T_2 bright volume to the enclosed T_1 enhancing volume in GBM: (a) CUBE FLAIR images depicting perilesional oedema, (b) calculated 3D-T_2 bright volume (147.62 cm^3), (c) T_1W post-contrast showing Rt parietal enhancing GBM with internal necrosis, and (d) calculated 3D-T_1-enhancing volume including internal necrosis (41.03 cm^3). *EGFR, endothelial growth factor receptor*; GBM, glioblastoma multiformes.

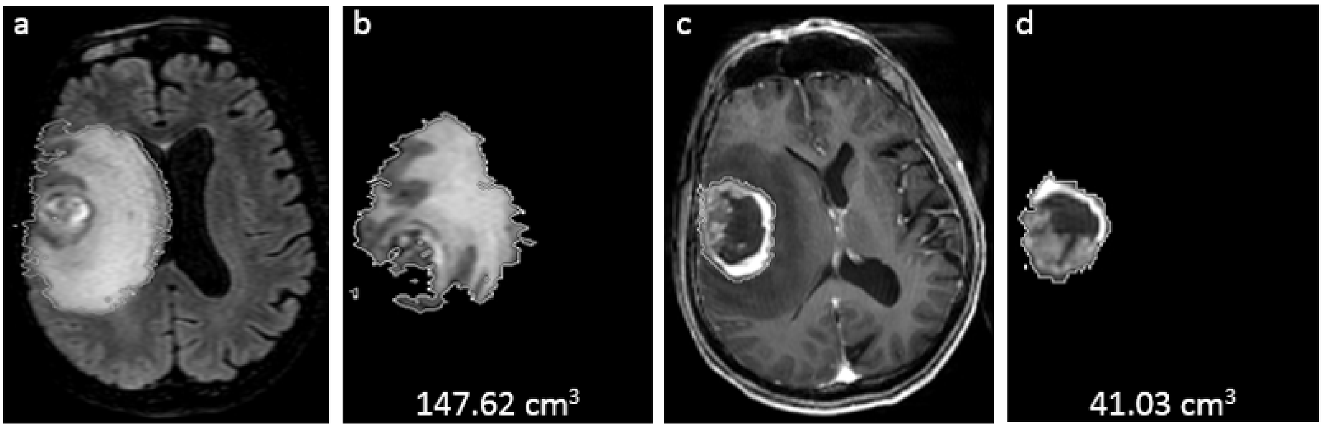
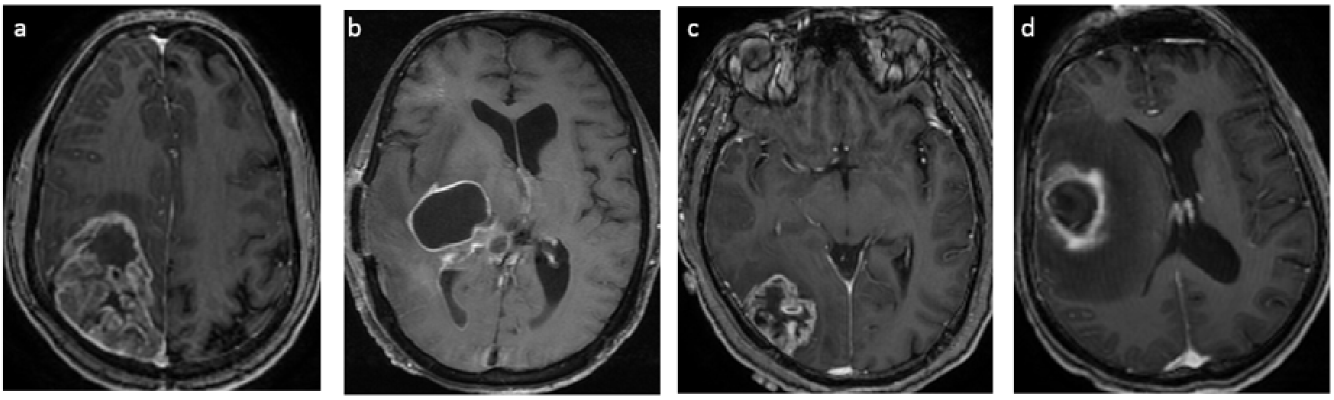


Figure 3. MRI post-gadolinium images of various grade IV GBM with hypermethylated and unmethylated *MGMT*. Imaging features showing: (a) mixed-nodular in a patient with hypermethylated *MGMT* and (b) ring enhancement in unmethylated *MGMT*. Another two cases demonstrating (c) preferential location of grade IV GBM with hypermethylation of the *MGMT* promoter located in parietal and occipital lobes, and (d) unmethylated of the *MGMT* promoter in the temporal lobes. GBM, glioblastoma multiformes; *MGMT*, O_6*-methylguanine-DNA-methyltransferase*.



changes.[7,51,69] *TP53* mutations are mainly found in astrocytomas and are associated with poor survival.[61] High incidence of *IDH1* mutations are seen in *TP53* mutations in early gliomagenesis of LGG.[61] GBMs with *TP53* mutations were reported to be smaller in size compared to the wild type, presented as areas that were hyperintense on T_2W FLAIR images.[7]

Ki-67 protein

The Ki-67 antigen is a nuclear protein encoded by *MKI67* gene, that is used as a histopathological indicator of cellular proliferation and growth.[62,63] Ki-67 is identified in paraffin-embedded sections made with the monoclonal antibody MIB-1.[62,63,70] The

Figure 4. MRI features of various grade IV GBM patients with *IDH1* mutation. The features included T_2W images showing (a) large size at time of diagnosis (b) multifocality, and (c) cystic components. (d) Post-gadolinium T_1W showing non-enhancing solid tumour component, (e) greater frequency of contact with the ventricles, and *(f) usually less necrotic (<50% of tumour volume, and (g) T_2 FLAIR showing less perilesional oedema (<50% of tumour volume). GBM, glioblastoma multiformes; *IDH1*, *isocitrate dehydrogenase 1*.

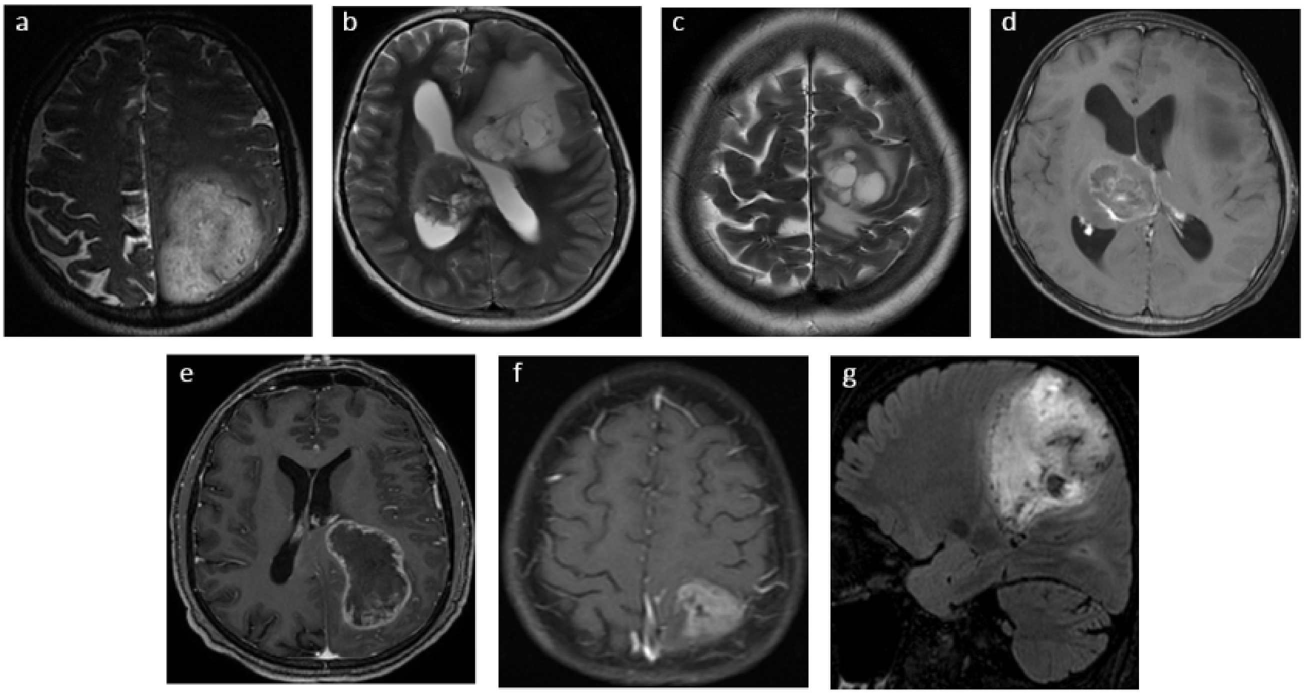


Figure 5. MRI features of grade III ODG patients with of *1p/19q* co-deletion. Imaging findings showing: (a) indistinct borders on T_1W, (b) GRE sequence with paramagnetic susceptibility and calcification and, (c-d) mixed signal intensities on T_1W and T_2W. GRE, gradient echo; ODG, oligodendroglioma.

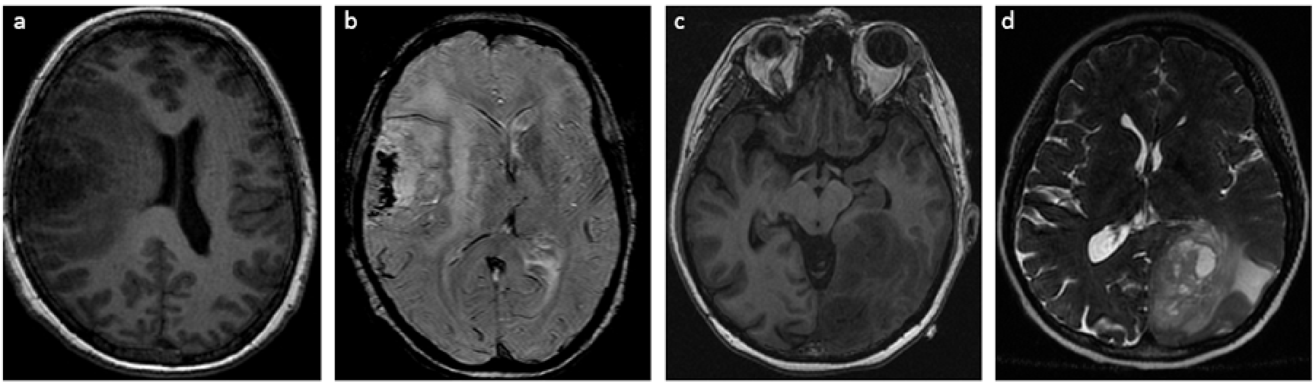
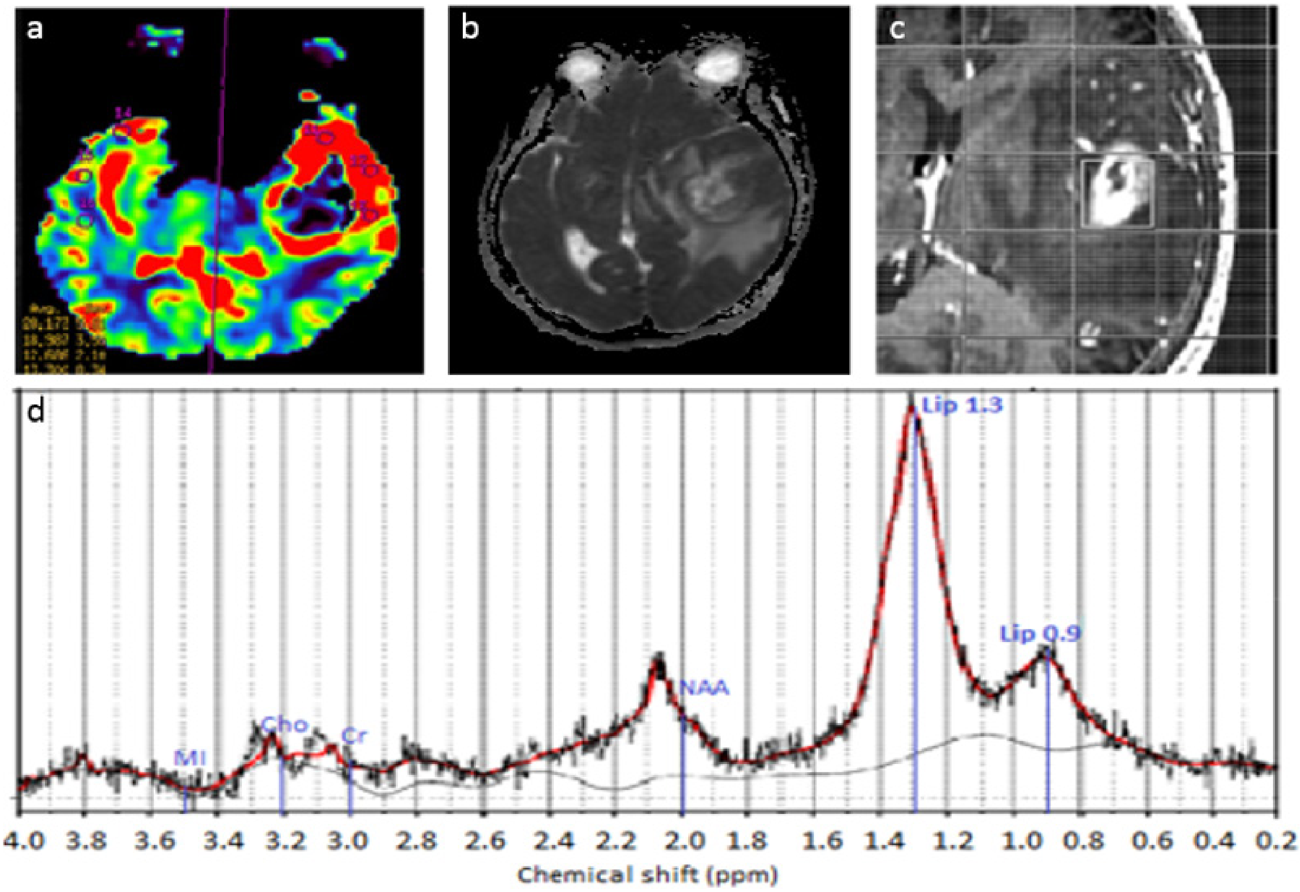


Figure 6. The MRI images of a grade IV GBM with prominent palisading necrosis, microvascular proliferation, Ki-67 index ~15–20% in a few cellular areas. Imaging findings showing: (a) relative CBV colour map where high blood volume was seen at the rim area, (b) decreased ADC shown as hypointense area compared to CSF in tumour region, (c) the voxel placement in SVS, and (d) the corresponding brain spectra acquired using LC Model where MI, Cho, Cr, NAA & Lip peaks are labelled. Elevated lipid peaks and Cho, with decreased NAA were apparent in the spectrum. ADC, apparent diffusion co-efficient; CBV, cerebral blood volume; Cho, choline; Cr, creatine; CSF, cerebrospinal fluid; GBM, glioblastoma multiformes; Lip, lipid; MI, myo-inositol; NAA, N-acetyl aspartate; SVS, single voxel spectroscopy.



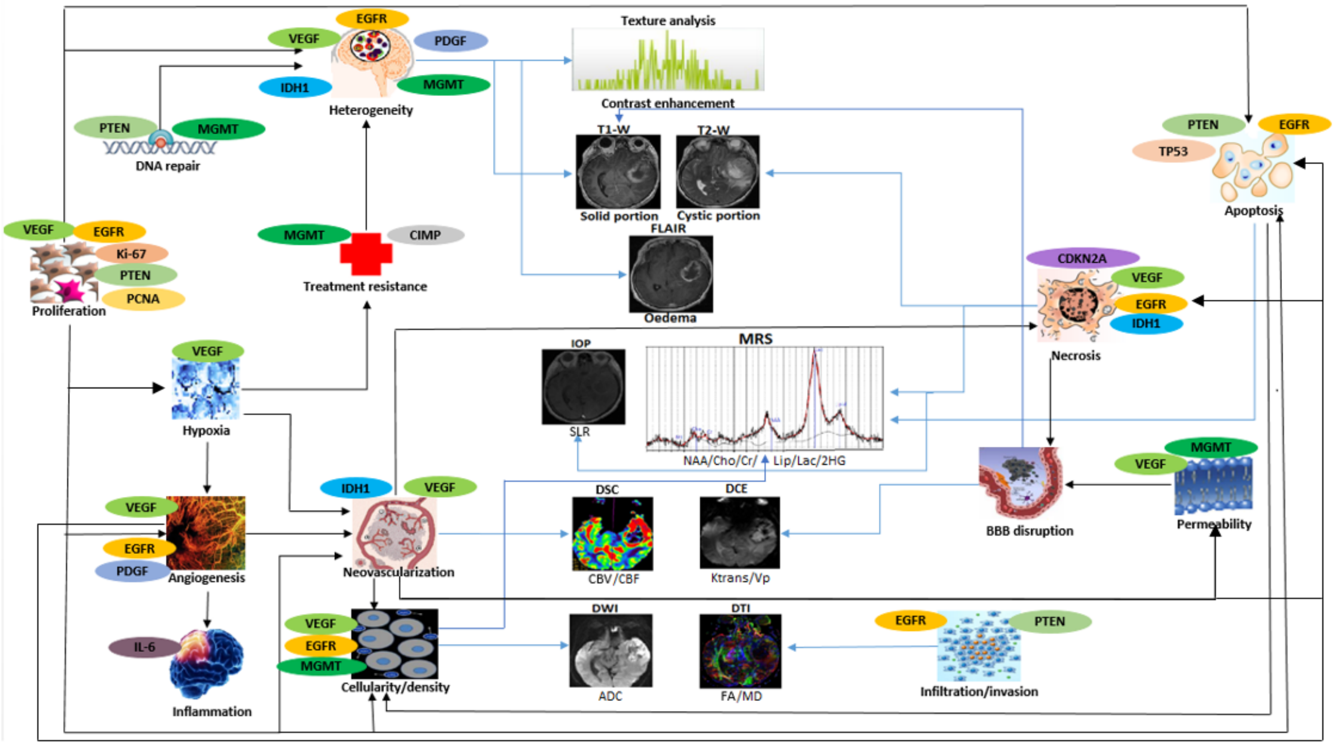


Figure 7. Radiogenomic approach for glioma characterisation. A schematic diagram to illustrate the relationship of glioma morphology with gene expressions and imaging characteristic. Black arrows indicate associations between different glioma morphology while blue arrows represent the linking between glioma morphology and MRI. The images displayed are for visual guide only. ADC, apparent diffusion co-efficient; BBB, blood-brain barrier; CBF, cerebral blood flow;CBV, cerebral blood volume; CDKN2A,*cyclin-dependent kinase inhibitor;* Cho, choline*; Cr, creatine;* DCE, dynamic contrast-enhanced; DSC, dynamic susceptibility contrast; DWI, diffusion-weighted imaging; DTI, diffusion tensor imaging; *EGFR*, *endothelial growth factor receptor*; FA, fractional anisotropy; *IDH1*, *isocitrate dehydrogenase 1*; IOP, in and opposed-MRI; K_{trans}, volume transfer constant; Lac, lactate; Lip, lipid; MD, mean diffusivity; *MGMT*,*O_6-methylguanine-DNA-methyltransferase*; MRS, magnetic resonance spectroscopy; NAA, N-acetyl aspartate; *PCNA, proliferating cell nuclear antigen*; *PDGF*, *platelet-derived growth factor*; *PTEN*, *phosphatase and tensin homolog*; SLR, signal loss ratio; *VEGF*, *vascular endothelial growth factor; VP, plasma volume*.

Ki-67 index is measured as the percentage of positively stained nuclei.[71] A high Ki-67 index correlates positively with tumour grades and prognosis (overall survival).[30]

High proliferation activities suggested as the elevation of Ki-67 index are related to higher relative CBV in GBM.[13] In linkage with water mobility heterogeneity, an inverse correlation is seen between Ki-67 index with ADC across glioma grades[9,30,70,71] (Figure 6). Positive correlations are also seen between metabolite alterations of choline (Cho/Cr), lactate over creatine ratio (Lac/Cr) and MI with Ki-67 index.[49,71,72] Elevated Cho with cell proliferation and malignancy was linked to oncogenic transformation triggered by hypoxia[19,31,49,55,62] while the decrease in Cho levels was related to necrosis. Lac is the product of anaerobic glycolysis while MI is a marker for glial cells.

Other candidate genes as radiogenomic markers

Although less significantly associated, other genes have also been linked as potential radiogenomic markers and are discussed below.

Vascular endothelial growth factor (*VEGF*) *gene*, encodes the vascular endothelial growth factor, promotes endothelial proliferation, new blood vessel formation and growth of the new vessels into interstitial tissues.[9,11,38,62] Overexpression of *VEGF* has been linked to ODG progression[7] and associated with contrast-enhancing tumours, hypoxia, angiogenesis, and oedema in GBM.[9,33,73] Areas of non-enhancing tumour in GBM imply decreased vascular permeability corresponded with low *VEGF* levels.[60,74] Upregulated *VEGF* is also associated with malignancy and microvascular density[75] although no direct approach to quantifiable parameters found.

Platelet-derived growth factor (*PDGF*) is a growth factor that regulates cellular differentiation and responses to tissue damage.[76] *PDGF* overexpression has been reported for 11% in glioma of all grades[76,77] and indicates enriched oligodendrocytic signature in the proneural subtype of GBM.[39,51] In GBM, *PDGF* is linked to intratumoural heterogeneity evaluated using histogram and texture analysis by assessing the spread of the grey level values of image voxels and the spatial relationship of the pixels.[45,78–81]

PTEN (*Phosphatase and tensin homolog*) regulates cell proliferation, adhesion, invasion, apoptosis and DNA damage repair,[7,36,51] is downregulated in brain tumours. *PTEN* loss is frequently observed in the frontal lobe of the brain (86.3%), while *PTEN* deficiency is significantly higher in the left lateral ventricle (42.9%) of GBM patients.[35]

Cyclin-dependent kinase inhibitor (CDKN2A) codes for a protein that acts as a tumour suppressor by regulating the cell cycle.[69] *CDKN2A* deletions were reported at 42.6% in necrotic tumour of GBM patients.[7] The classic subtype of GBM also has a strong association with *CDKN2A* deletion (92%).[51]

Proliferating cell nuclear antigen (PCNA) codes a protein that aids leading strand synthesis during DNA replication. Overexpression of this gene has been implicated as an indicator of malignancy and poor prognosis in glioma.[39,49]

Another gene of interest is *Periostin*, where its upregulation is correlated with cellular invasion and oedema in GBM.[73] It induces invasion probably through epithelial-mesenchymal transformation, where high expression is observed in the mesenchymal GBM subtype that leads to poor survival. *CpG island methylator phenotype (CIMP)*-positive is also associated with poor prognosis and treatment response.[53]

DISCUSSION

This review discusses the recent advances in correlating genomic changes with imaging phenotypes. This may help clinicians to further appreciate the use of genomic information for characterisation of glioma and discrimination of glioma grades in facilitating treatment planning and management. While more work is needed to explore the molecular pathways further so that better correlations can be established, together with validation by other studies, this approach serves as an important and emerging area for an applied clinical use.

Targeted therapy

Tumour molecular heterogeneity not only varies across patients but also throughout a single tumour, indicating broad genetic alterations and adaptation to the microenvironment.[15] Genomic heterogeneity can cause treatment resistance and highly heterogeneous tumours have a higher tendency for tumour progression.[5] The radiogenomic approach enables identification of genes that are directly involved in cell growth, infiltration, proliferation, differentiation, apoptosis, neurogenesis, and synaptic transmission.[39] Activated oncogenic signalling pathway via genetic mutations in *EGFR*/P13K/Akt and Ras/RAF/MEK pathways are major drivers for tumorigenesis.[52] Targeting signalling pathway with tyrosine kinase inhibitors and using bevacizumab as a *VEGF* inhibitor are the targeted therapies being studied in GBM.[53,82] Inhibition of genes that regulate lipid metabolism to induce cell death makes a promising molecular target in treating malignant glioma.[82]

This review provides insights into possible radiogenomic markers that could reliably link the imaging features to molecular signatures of the tumours. The imaging features are potentially useful markers as non-invasive molecular surrogates to infer genetic expression profiles of tumour. The restructuring of WHO guideline recognises the importance of incorporating genetic features (*i.e., IDH1* status and *1p/19q* codeletion status) into histology for classification of the diffuse glioma.[2,3]

Current research indicates:

1. *EGFR* amplification/overexpression are associated with contrast enhancement in GBM, increase in perfusion metric, metabolite changes, and restricted water diffusion. High-grade gliomas, which are mostly heterogeneous with the presence of solid enhancing rim and cystic portion implies a higher possibility of *EGFR* amplification.
2. Hypermethylated *MGMT* tumours showed mixed-nodular enhancement, non-temporal lobe lesions, and often show radiation or treatment-induced pseudo-progression. Treatment management can be facilitated by assessment of *MGMT* methylation status of the patient to ensure effective treatment response in concomitant and adjuvant chemoradiotherapy with temozolomide.
3. Astrocytomas and ODG that harbour *IDH1* mutation exhibit more favourable prognosis and response to chemotherapy compared to the wild types. Thus, patients that benefit from chemotherapy could be identified. GBM with *IDH1* mutations are larger at diagnosis, may be multifocal with left frontal lobe predominance, may be non-enhancing, have cystic and diffuse components, have a greater frequency of contact with brain ventricles, infrequent vascular abnormalities, less extent of necrosis and oedema.
4. ODG with *1p/19q* loss demonstrated indistinct borders on T_1W images, mixed-signal intensities on T_1W & T_2W, paramagnetic susceptibility effect, calcification, elevated CBV, and infiltrative growth patterns.
5. Increased proliferation as indicated by elevated Cho/Cr ratio, restricted diffusion and increased lipid correspond with higher Ki-67 index in relation to increased proliferation activities.

Recommendations for future research

Integration of molecular imaging with MRI techniques offers insights into the genetics in glioma. Genetic changes lead to metabolic reprogramming of the biosynthesis of glucose, glutamine, lipids, protein, DNA, and RNA for rapid growth and cell division of the tumour.[52] Metabolite characteristics of GBM include enhanced glycolysis, elevated glutaminolysis and exacerbated lipogenesis. Potential research includes inhibiting glucose metabolism as regulated by *HK2, PKM2,* and *IDH*; and lipid metabolism as regulated by *sterol regulatory element binding protein*, *acetyl-CoA carboxylase*, *fatty acid synthase* and *low-density lipoprotein receptor*[52] as target for personalised treatment. The linkage between the genetic profile and imaging phenotype to implicate metabolite regulations is another potential radiogenomic study. The presence of lipid in brain tumours has sparked new interest in glioma lipidomics using lipid quantification.[34,82,83] Lipids have roles in necrosis, apoptosis,[84] cellular membrane breakdown[55] and signal transduction. The elevated lipid fractions quantified using MRS and in- and opposed-phase (IOP) are related to tumour aggressiveness.[11,31,34]

Further research in linking tumour characteristics such as metabolite changes, DTI and DKI metrics with molecular signatures could add more values to the understanding of gliomagenesis.[11,24] Quantification of angiogenesis and neovascularisation biomarkers with *VEGF* expression using PWI (*i.e.* CBV & permeability maps), arterial spin labelling (*i.e.* tumour blood flow) and intravoxel incoherent motion (IVIM) (*i.e.* molecular diffusion coefficient) will be of interest.[4,6,9,11,19,24–28,30,35,42,43,49,85] The association of *VEGF* and inflammatory marker, interleukin-6 (*IL-6*), is another potential research interest as angiogenesis is also highly related to inflammation.[75] Future works in the area of radiogenomics should explore molecular imaging, nanoparticle imaging, computer-aided detection, and targeted therapies. Most of the studies reported the comparison between binary groups (HGG *vs* LGG, or GBM *vs* control). Multiple group analysis should be done to compare the glioma grades to provide a better evaluation of the tumour characteristics.[34,86] Variation in imaging acquisition protocol among institutions, tumour sampling, different region of interests, and difficulties in matching the imaging dimension with molecular profiles are the major challenges for integration of imaging and molecular genetic features.

CONCLUSION

Our review provides insights into possible "personalised" imaging biomarker for precision therapy in glioma based on molecular signatures that provide fundamental information to facilitate decision-making by clinicians in determining treatment and management of tumour that will most likely benefit the patient.

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