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Quantitative Magnetic Resonance Imaging and Radiogenomic Biomarkers for Gliomas Characterisation: A Systematic Review

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Keywords: Radiogenomic, quantitative MRI, gliomas, biomarkers, imaging, genes

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Quantitative Magnetic Resonance Imaging and Radiogenomic Biomarkers for Gliomas Characterisation: A Systematic Review

Manuscript Type: Original Research (Systematic Review)
Abstract

Objectives: 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 molecular level. This review assembles recent evidence highlighting the value of using radiogenomic biomarkers to infer underlying biology of gliomas and correlation with imaging features.

Methods: 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 were relevant to molecular biomarkers linked to imaging biomarkers.

Results: Radiogenomic markers 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%). Summaries of the relationship of morphology with selected gene expressions and imaging characteristic, prognosis and therapeutic response were presented.

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

Advances in knowledge: Radiogenomics offer clinicians better insight into diagnosis, prognosis, and prediction of therapeutic responses of glioma.
Keywords: Radiogenomic, Radiomics, quantitative MRI, gliomas, biomarkers, imaging, genes

1. Introduction

Gliomas, which comprise of 27% of all brain tumours, are lethal primary malignant brain tumours originating from the interstitial tissue of the brain (1). Gliomas are categorized as diffuse astrocytic and oligodendrogial 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 features integrated molecular parameters into histology that underlines the importance of radiogenomic 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, magnetic resonance imaging (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, 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 serve as the gold standard but suffers from several drawbacks such as intra-and inter-observer 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 (DWI), perfusion-weighted imaging (PWI), diffusion tensor imaging
(DTI), diffusion kurtosis imaging (DKI) and magnetic resonance spectroscopy (MRS) are used to define tumour morphology and functionality (4, 11, 12).

Glioma detection and grading at its earliest stage are crucial for early intervention to improve prognosis and minimize neurocognitive risks. The problem of grading gliomas 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 gliomas.

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 intra-tumoural gene expression patterns that steer the unique characteristics and morphological manifestation of gliomas 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 characterize 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 personalized 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 characterizing gliomas. We plan to stratify radio-phenotypes that could serve as molecular surrogates to infer specific genetic expression patterns from the review.

2. Methods

2.1. Eligibility criteria and search strategy

We performed a systematic review on imaging biomarkers (radiogenomics) of the 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 selection of full-text articles. The detailed research questions were established using the patient, intervention, comparator, outcome and study design (PICOS) approach. The questions were devised as follows: What are the key genes associated to the imaging characteristics of gliomas? What are the changes of the gene expression patterns of the tumour? How are the specific gene expression patterns linked to specific MR imaging features? In addition, 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 randomized or cohort MRI studies of gliomas 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 independently by PS and reviewed by NR, JHDW, and AAA respectively.

2.2. Study selection and data extraction

Only studies published in English after 2002 were selected and the last search was on 30th October 2017. Relevant data regarding imaging features and molecular profiles was extracted from each article. The data collected was categorized into gene groups, associated with different imaging characteristics of tumour. The main findings of the studies were also recorded (Appendices A1).

3. Results

3.1. 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 are overlaps in both of the tables as some of the studies investigated several parameters.

3.2. Findings

Table 1 lists the quantitative MRI biomarkers that are reported in the literature reviewed. Figure 2-6 show the structural and functional images of gliomas of different grades acquired from conventional and advanced MRI techniques, in relation to gene expressions. We identified gene expression profiles linked to glioma characteristics defined in Table 2.
3.3 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, 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) (24). EGFR amplification in histologically pure anaplastic oligodendrogliomas (ODG) is indicative of GBM. EFGR overexpression indicated poor outcome and correlated with decreased overall survival in GBM (7, 25). 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 (26). 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 (27-29).
Contrast enhancement of the solid portion of tumour in T1-W (T1-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 part of the tumour and its surrounding tissues are comprised of actively proliferating cells such as invasive tumour cells, microglial cells and reactive astrocytes (30). In terms of enhancement, \( \text{EGFR} \) amplification/overexpression were associated with higher T1+C (post-contrast) and T2/FLAIR hyperintense volume, higher ratio of the contrast enhancing volume to the necrotic tumour volume and greater ratio of T2-bright volume to T1-enhancing volume (including internal necrosis) in GBM (24, 27, 31-34) (Figure 2). \( \text{EGFR} \) 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 (27, 35, 36). 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, 30, 37-41), and restricted water diffusion (27, 28) are also related to \( \text{EGFR} \) amplification/ overexpression/ mutation.

**\( \text{O6-Methylguanine-DNA-Methyltransferase (MGMT)} \)**

The second gene that appears most frequently in the studies reviewed (20.8%) is the \( \text{MGMT} \) gene and has been reported for 30%-60% in GBM. The \( \text{MGMT} \) gene encodes a DNA repair protein that is involved in cellular defence against mutagenesis and toxicity from alkylating agents (42). GBM with \( \text{MGMT} \) promoter methylation demonstrated more favourable prognosis in terms of longer median survival (6, 32, 43-45). GBM with \( \text{MGMT} \) promoter methylation showed better treatment response (6, 32) due to decreased \( \text{MGMT} \) protein
expression that reduces DNA repair activity against temozolomide, a DNA alkylating agent. Thus, the sensitivity to therapy improves due to increase in endothelial permeability that facilitates the penetration of drugs and their delivery (42, 43).

Hypermethylated MGMT tumours tend to have mixed-nodular enhancement, non-temporal lobe lesions and often show radiation or treatment-induced pseudo-progression (46). On the contrary, unmethylated MGMT tumours have high occurrence of temporal lobe lesions, ring enhancement and true progression (24) (Figure 3). Tumour characteristics such as cellular density, treatment response, and texture features are linked to MGMT methylation status (9, 32, 42, 43, 47). Increased ADC (apparent diffusion coefficient) values derived from DWI implicate changes in tumoural water diffusion incited from necrosis or apoptosis (38), and higher degree of spatial heterogeneity have been observed in contrast-enhancing unmethylated MGMT tumours (4, 9, 48). 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 (49).

**Isocitrate Dehydrogenase 1 (IDH1)**

The IDH1 gene 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, 50-53). IDH1 mutations are also one of the genetic features that indicate the proneural subtype of GBM (26) with better clinical prognosis in terms of overall survival and progression-free survival (44), and more favourable overall survival in diffuse astrocytomas and anaplastic astrocytoma (3, 50).
GBM with IDH1 mutations tend to be in the left frontal lobe, larger at diagnosis, may be multifocal, have increased 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 oligodendrogial morphology and also metabolite changes (24, 45, 53, 54) (Figure 4). Glioblastomas without IDH1 mutations showed larger volumes of contrast enhancement seen in T1-W +C (21, 24). The conversion to alpha-ketoglutarate by IDH1 gene is observable using MRS as elevation of 2-hydroxyglutarate (2HG) co-detected at 2.25ppm and 4.02 ppm that reflect changes in tumour cellularity (54, 55).

1p/19q codeletion status

The combined loss of chromosome arms 1p and 19q is uncommon in gliomas and is considered the earliest genetic hallmark of ODG whereby this change is seen in 50-70% of the neoplasms (56). Whole-arm 1p/19q co-deletion is a molecular evidence of ODG (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 (57, 58).

In conventional MRI studies, ODG with 1p/19q loss are more likely to have indistinct borders on T1-W images, mixed-signal intensities on T1-W and T2-W, paramagnetic susceptibility effect, calcification and infiltrative growth patterns (56, 59) (Figure 5). Elevated relative CBV with 1p/19q codeletions suggested increased neovascularity in gliomas with oligodendrogial components (58). 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 (57).
**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 changes (7, 26, 60). TP53 mutations are mainly found in astrocytomas and are associated with poor survival (50). High incidence of IDH1 mutations is seen in TP53 mutations in early gliomagenesis of LGG (50). GBMs with TP53 mutations were reported to be smaller in size compared to the wild type, presented as areas that were hyperintense on T2-W 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 (51, 52). The protein Ki-67 is identified by the Ki-67 index of paraffin-embedded sections made with the monoclonal antibody MIB-1 (51, 52, 61). The index was measured as the percentage of positively stained nuclei (62). The high expression of Ki-67 index correlated positively with tumour grades and prognosis (overall survival) (63).

High proliferation activities are related to vascularization via higher relative CBV in elevated Ki-67 index in GBM (13). In linkage with water mobility heterogeneity, an inverse correlation is seen between Ki-67 index with ADC across glioma grades (9, 61-63) (Figure 6). Positive correlations are also seen between metabolite alterations of choline (Cho/Cr), lactate over creatine ratio (Lac/Cr) and myo-inositol (M1) with Ki-67 index (38, 62, 64). Elevated Cho with cell proliferation and malignancy was linked to oncogenic transformation triggered by
hypoxia (19, 30, 37, 38, 51) 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, 31, 51). Overexpression of VEGF has been linked to ODG progression (7) and associated with contrast-enhancing tumours, hypoxia, angiogenesis, and oedema in GBM (9, 65, 66). Areas of non-enhancing tumour in GBM, implies decreased vascular permeability corresponded with low VEGF levels (45, 67). Upregulated VEGF is also associated with malignancy and microvascular density (68) although no direct approach to quantifiable parameters found.

*Platelet-derived Growth Factor (PDGF)* is a growth factor that regulates cellular differentiation and response to tissue damage (69). PDGF overexpression has been reported for 11% in gliomas of all grades (69, 70) and indicated enriched oligodendrocytic signature in the proneural subtype of GBM (26, 33). 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 (47, 71-74).

*PTEN*, which regulates cell proliferation, adhesion, invasion, apoptosis and DNA damage repair (7, 26, 27), is down-regulated in brain tumours. PTEN loss was observed frequently in the
frontal lobe of the brain (86.3% incident) while $PTEN$ deficient was significantly higher in the left lateral ventricle (42.9% incident) of GBM patients (24).

*Cyclic-Dependent Kinase Inhibitor (CDKN2A)* codes for a protein that acts as a tumour suppressor by regulating the cell cycle (60). $CDKN2A$ 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%) (26).

*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 for malignancy and poor prognosis in gliomas (33, 38).

Another gene of interest is *Periostin*, where its upregulation is correlated with cellular invasion and oedema in GBM (66). It induces invasion probably through epithelial-mesenchymal transformation, where high expression is observed in mesenchymal GBM subtype that leads to poor survival. *CpG island methylator phenotype (CIMP)-positive* is also associated with poor prognosis and treatment response (32).

4. 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 gliomas 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, with some of the studies need to be replicated, this serves as an important and emerging area for an applied clinical use.

4.1. 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 (33). Activated oncogenic signalling pathway via genetic mutations in $EGFR/P13K/Akt$ and Ras/RAF/MEK pathways are major drivers for tumorigenesis (29). Targeting signalling pathway with tyrosine kinase inhibitors and using bevacizumab as a $VEGF$ inhibitor are the targeted therapies being studied in GBM (32, 75). Inhibition of genes that regulate lipid metabolism to induce cell death makes a promising molecular target in treating malignant gliomas (75).

This review provides insights on possible radiogenomic markers that could reliably link the imaging features to molecular signatures of the tumours. The imaging features are potential useful markers as non-invasive molecular surrogates to infer genetic expression profiles of tumour. The restructuring of WHO guideline recognizes the importance of incorporating genetic features (i.e. IDH1 status and 1p/19q codeletion status) into histology for classification of the diffuse gliomas (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 greater frequency of contact with brain ventricles, infrequent vascular abnormalities, less necrosis, and oedema.

4) ODG with 1p/19q loss demonstrated indistinct borders on T1-W images, mixed-signal intensities on T1-W & T2-W, paramagnetic susceptibility effect, calcification, elevated CBV and infiltrative growth patterns.

5) Increased proliferation as indicated by elevated Cho/Cr ratio, restricted diffusion and lipid correspond with higher Ki-67 index in relation to increased proliferation activities.

4.2. Recommendations for future research

Integration of molecular imaging with MRI techniques offers insights on the genetics in gliomas. 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 (29). Metabolite characteristics of GBM include enhanced glycolysis, elevated glutaminolysis and exacerbated lipogenesis. Future research into glucose metabolism as regulated by $HK2$, $PKM2$, ...
and IDH; and lipids metabolism as regulated by Sterol Regulatory Element Binding Protein (SREBP), Acetyl-CoA carboxylase (ACC), Fatty acid synthase (FAS) and Low-Density Lipoprotein Receptor (LDLR) (29) may add to the radiogenomic. The linkage between the genetic profile and imaging phenotype to implicate metabolite regulations is another potential radiogenomic study. The presence of lipids in brain tumours has sparked new interest in glioma lipidomics using lipid quantification (75-77). Lipids have roles in necrosis, apoptosis (78), cellular membrane breakdown (37) and signal transduction. The elevated lipid fractions quantified using MRS and in- and opposed-phase (IOP) are related to tumour aggressiveness (11, 30, 77).

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 (11,81). Quantification of angiogenesis and neovascularization 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, 38, 42, 63, 79-85). The association of VEGF and inflammatory marker, interleukin-6 (IL-6), is another potential research interest as angiogenesis is also highly related to inflammation (68). Future works in the area of radiogenomics should explore the advances of molecular imaging, nanoparticle imaging, computer-aided detection, and targeted imaging of 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 (77, 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.

5. Conclusion

Our review provides insights to possible "personalized" imaging biomarker for precision therapy in gliomas 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.

Figure Legends

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

Figure 2: A case of grade IV GBM with EGFR amplification/overexpression. MRI features showing greater ratio of T2-bright volume to the enclosed T1-enhancing volume in GBM: a) CUBE FLAIR images depicting peri-lesional edema, b) calculated 3D- T2 bright volume (147.62 cm$^3$), c) T1W post contrast showing Rt parietal enhancing GBM with internal necrosis, and d) calculated 3D-T1-enhancing volume including internal necrosis (41.03 cm$^3$).

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 2 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.

**Figure 4: MRI Imaging features of various Grade IV GBM patients with IDH1 mutation.**
The features included T2W images showing a) large size at time of diagnosis b) multifocality, and c) cystic components. d) Post gad T1W showing non-enhancing solid tumor component, e) greater frequency of contact with the ventricles, and f) usually less necrotic (<50% of tumor volume, and g) T2 FLAIR showing less perilesional edema (<50% of tumor volume).

**Figure 5: MRI imaging features of Grade III ODG patients with of 1p/19q co-deletion.**
Imaging findings showing: a) indistinct borders on T1-W, b) GRE sequence with paramagnetic susceptibility and calcification and, c-d) mixed signal intensities on T1-W and T2-W.

**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 tumor region, c) the voxel placement in SVS (Single Voxel Spectroscopy), and d) the corresponding brain spectra acquired using LCModel where MI (myoinositol), Cho (choline), Cr (creatine), NAA (N-acetylaspartic acid) & Lip (lipid) peaks are labelled. Elevated lipid peaks and Cho, with decreased NAA were apparent in the spectrum.
**Figure 7: Radiogenomic approach for gliomas characterization.** A schematic diagram to illustrate the relationship of gliomas 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 MR imaging. The images displayed are for visual guide only.

**References**

60. CDKN2A gene (cyclin dependent kinase inhibitor 2A): US National Library of Medicine (NIH); [cited 2017 15 Nov].
Figure 1

- Records identified through database searching (n = 214)
- Additional records identified through other sources (n = 38)
- Duplicate records removed (n = 3)

- Records screened (n = 249)
- Records excluded (n = 170) (149 from titles screened, 17 from abstracts screened with 4 abstracts were not available)

- Full-text articles assessed for eligibility (n = 79)
- Full-text articles excluded, with reasons (n = 20)

- Studies included in qualitative synthesis (n = 59)
- Studies that did not investigate quantifiable biomarkers (n = 21)
  - Imaging biomarkers (n = 14)
  - Radiogenomic biomarkers (n = 24)

- Studies included in quantitative analysis (n = 38)
Figure 2

(a) Image with measurements: 147.62 cm³
(b) Image with measurements: 41.03 cm³
Table 1: The quantitative MR imaging biomarker of the included studies.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Imaging biomarkers *</th>
<th>Techniques</th>
<th>Number of studies</th>
<th>Ref</th>
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<tr>
<td><strong>Heterogeneity</strong></td>
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<td>Enhancement and necrosis</td>
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<td>[4]</td>
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<td><strong>Vascularity</strong></td>
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<td>Uncorrected CBV ratio and FPS ratio</td>
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<td>MRI+ PWI</td>
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<td>[81]</td>
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<tr>
<td>Min and max relative CBV and relative CBF</td>
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<td>(DSC / DCE)</td>
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<td>( K_{\text{trans}} ) and ( V_e )</td>
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<tr>
<td>Peak height in ET &amp; non-ET</td>
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<td></td>
<td>[85]</td>
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<tr>
<td><strong>Non-Gaussian diffusion/ Cell density/ cellularity</strong></td>
<td>ADC, slow diffusion coefficient (( D_{\text{slow}} )), distributed diffusion coefficient (DDC) and heterogeneity index (( \alpha ))</td>
<td>MRI+DWI / IVIM</td>
<td>3</td>
<td>[4, 48, 63]</td>
</tr>
<tr>
<td><strong>Infiltrations along WM tracts/ micro-vascularity</strong></td>
<td>FA, MD, and tensor decomposition p &amp; q maps &amp; functional diffusion maps (fDM) Relative anisotropy and radial diffusivity Diffusion trace in ET</td>
<td>MRI + DTI</td>
<td>6</td>
<td>[30, 49, 84, 87]</td>
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<tr>
<td><strong>Metabolite changes</strong></td>
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<td>MRI+ MRS</td>
<td>3</td>
<td>[11]</td>
</tr>
<tr>
<td>Lip/tCho</td>
<td></td>
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<td></td>
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<tr>
<td>Cho/Cr, MI/Cr, LL/Cr, NAA/Cr</td>
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<td></td>
<td></td>
<td>[30]</td>
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<tr>
<td>Lipid quantification: Signal loss ratio in solid and cystic subregions</td>
<td>MRI+MRS+IOP</td>
<td>3</td>
<td>[77]</td>
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<tr>
<td><strong>Kurtosis</strong></td>
<td></td>
<td>DKI</td>
<td>1</td>
<td>[11]</td>
</tr>
</tbody>
</table>

*only biomarkers that are statistically significant (p<0.05) are reported.

MRI refers to structural MRI (T1-weighted, T2-weighted and Fluid Attenuation Inversion Recovery (FLAIR) sequences).

DWI=diffusion-weighted imaging; PWI=perfusion-weighted imaging; DTI=diffusion tensor imaging; DKI=diffusion kurtosis imaging; IOP=in-and opposed-MRI; MRS=magnetic resonance spectroscopy; IVIM=intravoxel incoherent motion; ADC=Apparent diffusion; CBF=cerebral blood flow; CBV=cerebral blood volume; ET=enhancing tumour; FA=Fractional anisotropy; FPS=first-pass slope; \( K_{\text{trans}} \)= Volume transfer constant; MD=mean diffusivity; \( V_e \)= volume of extravascular extracellular space per unit volume of tissue; WM=white matter; Lip=lipid; Cho: choline; Cr=creatine; MI=myoinositol; LL=lactate: NAA=N-acetyl aspartate
Table 2: The radiogenomic biomarkers linking imaging features/phenotypes and gene expression patterns of the included studies.

<table>
<thead>
<tr>
<th>Molecular biomarkers</th>
<th>Characteristics</th>
<th>Imaging biomarkers</th>
<th>Number of studies</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EGFR</strong></td>
<td>Diffusion</td>
<td>rCBV, PSR</td>
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<td>[13]</td>
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<tr>
<td></td>
<td>Morphology</td>
<td>Anatomic location (radiogenomic maps)</td>
<td></td>
<td>[24, 27]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Percentage of CE, NE, necrosis &amp; edema and largest diameter on lesion</td>
<td></td>
<td>[7]</td>
</tr>
<tr>
<td></td>
<td>Morphology, diffusion &amp; interaction with ECM</td>
<td>Border sharpness, restricted water diffusion, ADC</td>
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<td>[28]</td>
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<tr>
<td></td>
<td>Gene expressions</td>
<td>CE, necrosis, mass effect, edema, cortical involvement, CE:N volume ratio, T2 heterogeneity</td>
<td></td>
<td>[31]</td>
</tr>
<tr>
<td></td>
<td>Perfusion</td>
<td>VP &amp; K&lt;sub&gt;trans&lt;/sub&gt;</td>
<td></td>
<td>[36]</td>
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<tr>
<td></td>
<td></td>
<td>Normalized CBV &amp; CBF</td>
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<td>[35]</td>
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<td></td>
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<td>Mean &amp; relative TBF</td>
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<td>[80]</td>
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<tr>
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<td>Perfusion</td>
<td>K&lt;sub&gt;trans&lt;/sub&gt;</td>
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<td>Morphology</td>
<td>Normalized CBV</td>
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<td>Textures</td>
<td>Anatomic location</td>
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<td>[24, 43]</td>
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<td></td>
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<td>Correlation, energy, entropy &amp; local intensity</td>
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<td>[47]</td>
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<tr>
<td><strong>IDH1</strong></td>
<td>Morphology</td>
<td>Location</td>
<td>4</td>
<td>[24]</td>
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<tr>
<td></td>
<td></td>
<td>Percentage of CE, NE, necrosis &amp; edema and largest diameter on lesion</td>
<td></td>
<td>[7]</td>
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<tr>
<td></td>
<td>Metabolite change</td>
<td>2-hydroxyglutarate (2HG) &amp; TBF</td>
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<td>[54, 55]</td>
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<tr>
<td><strong>TP53</strong></td>
<td>Morphology</td>
<td>Percentage of CE, NE, necrosis &amp; edema and largest diameter on lesion</td>
<td>2</td>
<td>[7]</td>
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<tr>
<td></td>
<td>Gene expressions</td>
<td>CE, necrosis, mass effect, edema, cortical involvement, CE:N volume ratio, T2 heterogeneity</td>
<td></td>
<td>[31]</td>
</tr>
<tr>
<td><strong>PTEN loss</strong></td>
<td>Morphology</td>
<td>Anatomic location</td>
<td>2</td>
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<tr>
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<tr>
<td><strong>1p19q codeletions</strong></td>
<td>Vascularization</td>
<td>rCBV</td>
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<tr>
<td><strong>GAP4 and WWTR1 genes</strong></td>
<td>Intensities (ROI), sharpness of lesion boundaries, boundary shapes</td>
<td>Edge sharpness of necrotic portion</td>
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<td>[66]</td>
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<tr>
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<td>Proportion of enhancing tumour &amp; T1/FLAIR ratio</td>
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<td>[83]</td>
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<td>Edema/invasion FLAIR volumes</td>
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<td>[83]</td>
</tr>
</tbody>
</table>

Percentage of CE, NE, necrosis & edema and largest diameter on lesion

PSR=percent signal recovery, TBF=tumour blood flow, Ktrans=volume transfer constant; VP=plasma volume; VEGFR=vascular endothelial growth factor receptor; MGMT=O6-methylguanine-DNA-methyltransferase; IDH1=isocitrate dehydrogenase 1; PTEN=phosphatase and tensin homolog; EGFR=Epidermal growth factor receptor; TP53=tumour protein p53; Ki-67=Ki-67 antigen; PDGFA=platelet-derived growth factor; ROI=region of interest; CE=contrast enhancement; NE=non-enhanced; ECM=extracellular matrix; CE:N=contrast-enhancing volume to the necrotic tumour volume ratio
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