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Imaging Signatures of Glioblastoma Molecular Characteristics: A Radiogenomics Review

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Abstract

Over the past few decades, the advent and development of genomic assessment methods and computational approaches have raised the hopes for identifying therapeutic targets that may aid in the treatment of glioblastoma. However, the targeted therapies have barely been successful in their effort to cure glioblastoma patients, leaving them with a grim prognosis. Glioblastoma exhibits high heterogeneity, both spatially and temporally. Existence of different genetic sub-populations in glioblastoma allows this tumor to adapt itself to the environmental forces. Therefore, patients with glioblastoma respond poorly to the prescribed therapies, as treatments are directed towards the whole tumor and not to the specific genetic sub-regions. Genomic alterations within the tumor develop distinct radiographic phenotypes. In this regard, magnetic resonance imaging plays a key role in characterizing molecular signatures of glioblastoma, based on regional variations and phenotypic presentation of the tumor. Radiogenomics has emerged as a (relatively) new field of research to explore the connections between genetic alterations and imaging features. Radiogenomics proffers numerous advantages, including non-invasive and global assessment of the tumor and its response to the therapies. In this review, we have summarized the potential role of radiogenomic techniques to stratify patients according to their specific tumor characteristics with the goal of designing patient-specific therapies.

Keywords

Radiogenomics; Glioblastoma; Magnetic Resonance Imaging; Molecular Signatures; Machine Learning; Radiomics

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INTRODUCTION

Glioblastoma is the most frequently occurring primary malignant brain tumor in adults, with a median patient survival of 12–15 months (1), which has moderately improved lately due to the emergence of tumor treatment fields (2). Only about 5% of patients survive past 5 years from the time of diagnosis (3). Glioblastoma is identified with distinctive features of local invasion and diffuse infiltration into the surrounding brain tissue (4), significant genomic instability, cellular proliferation, robust angiogenesis, resistance to apoptosis, and tendency for necrogenesis (5,6). This leads to high likelihood of recurrence, poor response to treatment, and morbidity.

Surgical resection is not curative for glioblastoma, and even after gross total resection of the apparent tumor followed by radiotherapy with concurrent and adjuvant chemotherapy, tumor progression occurs (7). One of the main reasons for treatment failure in glioblastoma lies in notable cytological and genetic intra-tumor heterogeneity (8). It has been indicated that various genetic sub-populations co-habit within glioblastoma (i.e., there exists spatial genetic heterogeneity), which trigger different radiographic appearances and hinder therapies that do not account for the whole cohabiting tumor sub-populations in a tumor (9,10).

Over the past decade, the advent of gene expression profiling has provided new insights about the molecular and mutational profile of glioblastoma (11). Accordingly, a growing body of evidence has shown that “integrated” histological and molecular (phenotypic and genotypic) features are required for diagnosis of diffuse gliomas, which led to the 2016 CNS WHO consensus for more accurate diagnosis and reduced inter-observer variability (12). This is useful for improved tumor classification and better harmonization of patient cohorts for identification of patients most likely to respond to targeted therapies.

For gene expression profiling of the tumors, biopsy or surgical resection is required. Biopsies are usually prone to sampling errors and cannot provide a comprehensive molecular characterization within the tumor (13). Radiogenomics is a relatively new paradigm formed to non-invasively obtain tumor molecular characteristics (e.g., gene expression profiles or mutations) by virtue of the tumor’s radio-phenotypical signature (14,15). In addition to pre-operative assessments, radiogenomics can be immensely helpful in monitoring longitudinal changes of the tumor in response to treatments and adaptation of treatment strategies (16). MRI, as an indispensable diagnostic tool for neuro-oncology, has provided a platform for genomics studies through radiogenomics.

This review discusses the role and potential of MRI in radiogenomic studies for analysis of patients diagnosed with glioblastoma. We first start with a brief introduction of genomics of glioblastoma and the principle of radiogenomics, followed by an overview of findings of radiogenomic studies. Consequently, the considerations and challenges of current radiogenomic studies, as well as future directions, are discussed.

GENOMICS OF GLIOBLASTOMA

Genomics has the potential to contribute in the management of glioblastoma in several ways, including aiding in precise diagnosis, identification of targetable driver mutations, clinical trial design, and subtyping (11). The use of molecular information led to the genetic and clinical distinction of primary (or *de novo)* from secondary glioblastoma, which arise from lower grades. Specific genetic alterations are different in primary and secondary glioblastoma: the *IDH1* mutation is particularly frequent in secondary glioblastoma and young patients. It is therefore used as a diagnostic marker of secondary glioblastoma, and provides superior information to clinical and/or pathological data (17). Furthermore, *TP53* mutations are highly common in secondary glioblastoma, while *EGFR* overexpression is frequent in primary ones. Additionally, *EGFR* amplification, *PTEN* mutation, and loss of chromosome 10 are predominant in primary glioblastoma (18,19). Genomic profiling further facilitates the diagnosis by rectifying pathological findings and prognosis (20) through *DNA* methylation stratification, both of which can immensely affect the treatment plan, e.g., by avoiding chemotherapy (21).

Genomic information can also be helpful in the identification of mutations favorable for targeted, personalized therapies, and in homogenizing patient populations in clinical trials. Although there have been rare encouraging cases, most of the designed targeted therapies have failed to make improvements in the management of glioblastoma (11,22). Molecular biomarkers could aid the oncologists in prescribing chemotherapy regimens that are most effective according to the given mutations or to enroll patients in relevant clinical trials.

The advent of technologies that can measure genomic information in cancer has raised the hopes for finding biomarkers that predict resistance to traditional therapies (23). While molecular analyses are worthwhile for the stratification of glioblastoma patients, there are challenges in their application when put into practice. The analysis is dependent on the tissue samples obtained by surgical resection or biopsy procedure and therefore limited by the time at which the tissue is collected and the spatial location of the sampled tissue within the heterogeneous tumor. Furthermore, sub-optimal genomic analysis techniques, the type, cost and depth of coverage of the assay, can impose challenges in multi-institutional clinical trials (24). MRI is a versatile tool that can aid in non-invasive uncovering of genomic alterations before biopsy or surgery and guiding targeted biopsies. It can be further incorporated in the whole management spectrum from detecting patient-specific therapeutic targets, monitoring treatment response, and prognosis.

RADIOGENOMICS OF GLIOBLASTOMA

Imaging genomics (or radiogenomics) can be performed to either understand any possible molecular associate of a specific radiographic phenotype, or indicate how a particular genomic variation might impact the imaging traits of the tumors (15,16,25). Radiogenomic studies are either exploratory or hypothesis-driven (16). In exploratory studies, a variety of imaging features are tested against several genomic alterations. On the other hand, in hypothesis-driven studies, for a specific genetic variation (gene mutation or pathway alteration), relevant radio-phenotypes are evaluated.

A radiogenomic study should ideally be designed based on a systematic approach comprising of several steps: 1) image acquisition, 2) image post-processing, including noise/artifact reduction, intensity and/or orientation standardization, co-registration of the multi-parametric MRI scans, 3) region-of-interest definition using manual annotation or (semi-)automatic segmentation, 4) feature extraction based on human-engineered (conventional radiomics) or deep learning approaches, and 5) data analysis for prediction of tumor genomics, involving machine/deep learning methods for feature selection, classification, and cross-validation. There are numerous leading review papers with detailed descriptions of these steps (8,26,27). A schematic flow-graph of a radiomics study is illustrated in Fig. 1 and the radiogenomic studies designed according to this workflow are summarized in Table 1.

While the mentioned analytical strategy should preferably be undertaken, there are only a few radiogenomics studies that have been carried out with this design. Here, we provide an overview of the radiogenomics studies according to their exploratory or hypothesis-based design, and their molecular characteristic of interest.

Exploratory Studies

Most of the existing radiogenomic studies are intended to establish relationships between the tumor radiographic characteristics (e.g., tumor enhancement volume, necrotic extent) and gene expression profiles or pathways. These exploratory studies aimed to build foundations for the best research design, data collection, and analysis to help in developing relevant hypotheses for future studies. As exploratory studies seek to find relevant mutations that may produce distinctive radiographic phenotypes, we have summarized the overview of these studies based on their investigated radio-phenotypical characteristics.

Tumor Core

Van Meter et al (28) explored intra-tumor genetic variations in regions located in the periphery of enhancing mass on *T1CE* and poorly-enhancing central tumor core. Using microarray technology, *RNA* sequencing was performed for specimens collected intra-operatively from the tumor periphery and the necrotic or pre-necrotic regions, via image-guided stereotactic biopsies. Significant differences were found for therapeutic targets like *EGFR* and *VEGF*. The results were suggestive of the existence of spatial variations in intra-tumor glioblastoma regions, with the enhancing tumor periphery having an increased expression of genes involved in proliferation and invasion events, and the poorly enhancing and low perfused core having an elevated rate of expression for hypoxia-induced genes.

In a study by Diehn et al (29) on 22 patients who underwent stereotactic localized biopsy sampling, the gene-expression profiles were shown to be discriminant between contrast enhancing and non-enhancing tissues. Furthermore, an infiltrative subtype of glioblastoma, which was specified by the presence of an infiltrative pattern in the edematous region, was significantly associated with the genes involved in *CNS* development and gliogenesis. This finding suggested a possibility of shared gene-expression programs between infiltrative glioblastoma subtype and glial progenitors or *CNS* stem cells. The tumor's mass effect was shown to be correlated with the genes associated with proliferation, and contrast

enhancement on *T1CE* images was shown to be related to the genes involved in hypoxic processes.

Pope et al (30) compared gene expressions based on *DNA* microarrays between incompletely-enhancing (IE) and contrast-enhancing (CE) tumors in newly diagnosed glioblastoma. 71 genes, including proangiogenic and edema-related genes including *VEGF*, showed overexpression in *CE* compared to *IE* glioblastoma. Several genes related to primary glioblastoma were expressed in *CE*, while a few genes related to secondary glioblastoma showed expression in *IE* glioblastoma, with the latter event being associated with longer survival.

Analysis of copy number variation in multicentric glioblastoma (defined by the presence of multiple foci of contrast enhancement on *T1w* images or multiple isolated lesions with high signal intensity on *T2-FLAIR* images) has revealed dissimilar gene expression profiling and signaling pathways in different foci of multicentric glioblastoma, which is suggestive of high intra-patient heterogeneity of molecular characteristics (31).

The volume of CE tumor on MRI, in addition to clinical and genomics factors (*HRAS* copy number variation) has also been reported to provide an accurate prognosis of survival in a cohort of 102 glioblastoma tumors (32).

Most of the radiogenomic studies have been carried out using correlation and/or statistical significance assessment. The first group to explore the relationship of radio-phenotypes with molecular pathways using a machine learning approach was Itakura et al (33). They included a multi-institutional cohort of 265 GBM patients (development cohort (n=121), validation cohort (n=144)), and calculated 388 image features from *T1CE* images. Three imaging phenotypes were identified using a clustering algorithm: pre-multifocal, spherical, and rim-enhancing. The pre-multifocal imaging phenotype with the worse survival was significantly associated with the c-Kit stem cell factor receptor pathway. The spherical phenotype with intermediate survival was linked to down-regulation of 21 pathways, including *VEGFR* and *PDGFR-α* signaling. The rim-enhancing phenotype with the favorable survival was differentiated by the up-regulation of 31 pathways, including *PDGFR-β* signaling and many of the down-regulated pathways in spherical phenotype, such as *VEGFR* signaling. This was further evaluated by Rathore et al (34), who found a relationship between these imaging subtypes with Verhaak's molecular subtypes of glioblastoma tumors (35).

Peritumoral Edematous/Tumor-Infiltrated Tissue

The high amount of non-enhancing peritumoral edematous/tumor-infiltrated tissue (appeared as hyperintense region on *T2-FLAIR* images) was used as the imaging characteristic in exploration of gene associations in a study by Zinn et al (36). They suggested that this edema/cellular invasion phenotype exhibits upregulated PERIOSTIN (*POSTN*) gene set and downregulated miR-219, which was predicted to bind to and regulate *POSTN*. The expression of *POSTN* was related to poor overall and progression-free survival. In a consecutive study, they proposed that the combination of tumor volume, age, and *KPS* (VAK) can provide a 3-point scoring system for classification of glioblastoma (37). They showed that the group with good prognosis (the so-called VAK-A) was significantly

associated with *p53* activation and favorable *MGMT* promoter methylation status, as compared to the poor prognosis class (VAK-B).

Jamshidi et al (38) carried out a preliminary study on 23 glioblastoma patients and showed an association of vasogenic edema with PI3K signaling network, and a correlation of SVZ involvement with Ras oncogene family members.

Necrotic Core

In a study on necrotic volumes extracted from MRI scans of 99 glioblastoma patients (30 female, 69 male), Colen et al (39) identified gender-specific molecular mechanisms for cell death (*TP53* apoptotic in male patients, *MYC* oncogenic in female patients), suggesting the importance of including sex as a covariate in analyzing molecular data, designing clinical trials, and planning therapies. This was one of the first radiogenomic studies highlighting sex-related variations in genomics and imaging characteristics of glioblastoma.

Using a correlation approach, Grossman et al (40) demonstrated association of necrotic volume with apoptosis and immune response, CE volume with signal transduction, and peritumoral edematous/tumor-infiltrated tissue with homeostasis.

Diffusion Restriction

Cui et al (41) conducted a multi-institutional study, in which high-risk volume (HRV) of glioblastoma, defined as the region with low cellularity according to *ADC*-map and high enhancement on *T1w* images, was tested against *MGMT* methylation status, and mutation status of multiple genes. HRV was not predictive of *MGMT* methylation status but their combination served as a strong predictor of the overall survival. Furthermore, HRV was significantly higher in the *PIK3CA*-mutant compared to the wildtype group.

Zinn et al (42) studied *ADC* values in the NE portion of the tumor, based on *T2-FLAIR* images, in 35 glioblastoma patients and found that more diffusion restriction (lower *ADC* values) in the peritumoral edematous/tumor-infiltrated tissue was correlated to distinct genomic networks and differentially-expressed genes that play a role in invasion.

Heiland et al investigated the role of DTI-derived parameters in identification of gene expression pathways (43) in 21 patients who underwent neuro-navigated biopsy operation. In the CE tumor region, *FA* was strongly associated with activation of epithelial-to-mesenchymal transition pathway and glioblastoma with high *FA* had the worse prognosis, *MD* was linked to the genes related to neural function and higher *MD* was suggestive of more favorable prognosis.

Angiogenesis

Barajas et al (44) collected multiple biopsies from CE and peritumoral non-enhancing regions. They observed elevated *CBV* and *PH* values, and decreased *PSR* and *ADC* values, within CE regions. According to RNA expression patterns obtained by microarray analysis, 6,653 genes were differentially expressed between the two biopsy specimen groups (CE vs NE). Genes associated with mitosis, angiogenesis, and apoptosis were significantly up-regulated in CE regions as compared to NE parts. Heiland et al showed that vessel size (*VS*)

is highly related to hypoxia, and Epithelial Growth Factor (*EGF*) pathway and Epithelial-to-Mesenchymal-Transition (*EMT*) were strongly linked to *CBV* (45). *CBV* and *CBF*-related radiomic features have shown to be significantly related to upregulation of *PDGF*, *EGFR*, and *VEGF* pathways and downregulation of *PTEN* pathway in a study by Kong et al (46).

Metabolic Function

Only a handful of exploratory studies have investigated MRS in association with genomic data. In a study on 20 glioblastoma patients, Heiland et al (47) explored the relationship between the concentration of metabolites derived from MRS and gene expression pathways. They found that gene expression pathways associated with oligodendrocytic and neural development were significantly correlated to *nNAA* metabolite (*NAA* in the tumor normalized to the contralateral healthy tissue); high *nCr* was found to be correlated to proneural glioblastoma subtype, and low *nCr* was related to mesenchymal subtype; *nGlx* was significantly linked to the gene expression profiles involved in hypoxia and cytoskeletal processes; low *nGlx* was associated to neural subtype, and its high value was related to the classical subtype. Patients with higher *nNAA* showed longer progression-free survival.

Hypothesis-Driven Studies

Hypothesis-driven studies on glioblastoma are carried out given a certain hypothesis, based on the assumption of variations of one or more genes, pathways, or molecular subtypes, and through exploring the relevant radio-phenotype that best represents the assumed genomics alteration. Glioblastoma harbors around 60 mutations, however, many of these mutations are only “passengers” and only a few are driver mutations (48), which will be explained further.

In what follows, we have categorized the studies based on the mutation of a gene of interest with a focus on the genes that are most relevant for diagnosis and/or targeted therapies, signaling pathways, or molecular subtypes in glioblastoma. A summary of the most repeatable imaging findings for molecular signatures can be found in Table 2.

Isocitrate Dehydrogenase1 (IDH1)

The *IDH1* enzyme, found primarily in the cytoplasm and peroxisomes, which are cellular structures that process numerous molecule types, convert isocitrate to ketoglutarate. This leads to production of NADPH molecule, which is important for many cellular processes, such as producing energy, and protecting cells from harmful molecules called reactive oxygen species. The *IDH1* gene is responsible for providing instructions for producing the *IDH1* enzyme. The *IDH1* mutation produces an oncometabolite called 2-hydroxy-glutarate (*2-HG*), which in turn affects hypoxia inducible factor 1α (*HIF-1*α). In glioblastoma, an elevation of *HIF-1*α is a factor in progression of tumor (49,50). *IDH1* mutations are frequent in younger patients with grade II gliomas or secondary glioblastoma, and are generally found to have more favorable prognosis with increased overall and progression-free survival than *IDH1*-wildtype tumors (49–51). *IDH1* status has been included in WHO 2016 classification guidelines, due to its significant prognostic importance in stratifying gliomas.

Several radiogenomic studies have suggested connections between the *IDH1* mutation with radio-phenotypic appearance of glioblastoma. Chang et al (52) demonstrated that small

regions of enhancement and larger proportion of non-enhancing tumor, cysts with low *T1* and suppressed *T2-FLAIR* signal intensity, and well-defined tumor margins are more predictive of *IDH1*-mutant tumors. Similarly, another research study suggested that large regions of NE tumor can predict *IDH1* mutations (53). Hong et al (54) indicated that *IDH1*-mutant patients have a larger volume of abnormality on *T2w* and higher ratio of the *T2w* to *T1CE* volumes. Additionally, higher mean *nADC* and longer progression-free survival was observed for *IDH1*-mutant tumors compared to wildtype. Yamashita et al (55) studied 55 patients (11 patients with *IDH1* mutations) and proposed that absolute tumor blood flow (derived from the *CBF* maps of ASL imaging), relative tumor blood flow (the ratio of *CBF* in the tumor ROI compared to contralateral normal tissue), necrosis area, and percentage of cross-sectional necrosis area inside the enhancing lesion (the proportional area of no enhancement within the largest cross-sectional area of enhancement) were significantly higher in the *IDH1*-wildtype group than in mutant group. No significant differences were found for minimum or mean ADC values in the enhancing regions of the tumor (*T1CE* enhancement).

With regard to tumor location, researchers have reported somewhat similar findings: In the work by Carrillo et al (53), *IDH1* tumors occurred more in the frontal lobe, which was also verified by Ellingson et al (56) who showed the prevalence of *IDH1*-mutant tumors in the left frontal lobe. In a study of a mixture of different glioma grades, Altieri et al (57) demonstrated that IDH1 mutations occur mainly in the right hemisphere and for *IDH1*-wiltype glioblastoma, temporal lobe is the main area of incidence (249 gliomas; 221 HGG and 28 LGG). Conversely, in another study of lower grade (199 grade II/III) gliomas on the lesion location for *IDH1/2* and *TERT* mutations, Arita et al (58) reported frontal, insular and temporal lobes as the incidence locations of *IDH1/2* mutants. Neyra et al (59) used a voxel-based lesion symptom mapping (VLSM) analysis, and investigated the association of several key genes with tumor location. They found a predominance of the *IDH1* mutation in the frontal lobe adjacent to the rostral extension of the lateral ventricles both lower grade gliomas and glioblastoma. Overall, *IDH1* mutations seem to be more frequently occurring in the frontal lobe.

As mentioned earlier, *2HG* is an oncometabolite that has a key role in altering the *HIF1A* levels leading to switching the tumor cell functions towards progression and malignancy. The *IDH1* mutation leads to production of *2HG* and increasing evidence supports *2HG* to be an optimal biomarker of the *IDH1* mutation. Accumulation of *2HG* in the tumors with an *IDH1* mutation can be noninvasively detected *in-vivo* by MRS (60–62), which is ideal compared to biopsy, as it does not impose any risks to the patient and can be repeated, it can cover different tumorous regions and consider the normal appearing brain as an internal reference tissue (63). This method seems to present a unique example of MR-based non-invasive detection of a tumor biomarker that is biologically well-supported. However, accurate diagnosis based on this method is dependent upon proper acquisition and quantification methods to avoid false positive results (61,64).

O^6-methylguanine-DNA Methyltransferase (MGMT)

MGMT is a protein coding gene that encodes O^6-alkylguanine *DNA* alkyltransferase, which is a DNA repair enzyme. *MGMT* is crucial for genomic stability and is involved in cellular defense against mutagenesis and toxicity from alkylating agents, which are potent carcinogens resulting in cell death, mutation, and cancer. Genome-wide methylation of *MGMT* may be associated with carcinogenesis and tumor progression, silencing of tumor suppressors such as *TP53* and *PTEN* (65,66). Methylation of *MGMT* promoter occurs in 35–45% of malignant gliomas (WHO grades III and IV) and is an important predictive biomarker for the patient's response to alkylating chemotherapy in glioblastoma. Particularly, *MGMT* promoter methylation could affect the decision for adjuvant chemoradiotherapy and temolozomide treatment for elderly patients, as it could be too toxic for this patient population (67). For elderly patients with *MGMT* methylated high-grade gliomas, when temozolomide treatment was adopted, the overall survival improved and for unmethylated group, only radiotherapy is more efficient (68). Progression time is proposed to be significantly longer in patients with *MGMT* promoter methylation (21.9 months) compared to the unmethylated group (9.2 months), and pseudo-progression, which is a result of treatment-induced blood brain barrier disruption, is more frequent in *MGMT* methylated group. This in fact reflects the effectiveness of radiotherapy followed by temolozomide therapy for the patients with *MGMT* methylation and has shown to increase the overall survival in this patient group (69).

Prediction of *MGMT* methylation status, based on MRI, seems to be challenging but if successful, it will provide a worthwhile non-invasive diagnostic methodology for patient stratification and treatment planning, compared to biopsy. In this regard, Ahn et al (70) found that *MGMT* methylation was not significantly associated with any features on conventional MRI or DCE-MRI-derived K_{ep} and V_e or DTI-derived *ADC* and *FA*. However, K^{trans} was statistically higher in *MGMT* methylated group. As methylated glioblastoma tumors indicate more favorable prognosis, the increased K^{trans} in the tumor for this group could be attributed to better penetration of the drugs leading to a better response to treatment.

Rundle-Thiele (71) indicated that minimum *ADC* was strongly correlated to *MGMT* status and its elevation was highly suggestive of methylation. According to Chang et al (52), for the *MGMT* methylated group, heterogeneous nodular enhancement, presence of eccentric cyst, higher portion of non-enhancing tumor with cortical involvement, and slight frontal location dominance can be observed. Texture features from *T2w* imaging in a work by Korfiatis et al (72) could predict *MGMT* methylation status in 155 patients with 85% accuracy whereas Li et al (73) built a radiomic model with an accuracy of 80% based on features extracted from a combination of *T1w*, *T1CE*, *T2w* and *T2-FLAIR* images for prediction of *MGMT* status in 133 patients.

Kickingereder et al (74) in a study on 181 GBM patients, reported on added value of radiomics to *MGMT* status and clinical information for improving the prediction of overall and progression-free survival of patients by around 10%. This was similarly verified by Bae et al (75).

The most frequent location of *MGMT*-methylated glioblastomas seems to be the left temporal lobe (56,76) or the parietal lobe (57), and the *MGMT* unmethylated group prevail in the insular lobe. *MGMT*-methylated tumors with an *IDH1* mutation mostly grows in the left frontal lobe (56).

Platelet-Derived Growth Factor (PDGF)

*PDGF*s and their receptors (*PDGFR*s) play a critical role in cell growth and division, blood vessel formation, proliferation of mesenchymal cells, cell migration, and response to damage. *PDGF* gene encodes receptor tyrosine kinases (*RTK*s), a type of cell surface receptor, which transmits signals from cell surface into the cell via signal transduction (77,78). Amplification of *PDGF* and *PDGFR* genes, rearrangement of *PDGFR-α* or overexpression of *PDGF* ligand, are the common mutations in ~10% of glioblastoma (79). *PDGF* expression has been shown to be associated with negative prognostic markers of glioblastoma, such as age and lack of the *IDH1* mutation (11,80).

A study by Gutman et al (81) suggested that *PDGFR-α* could be predicted by the ratios of hyperintensity/total tumor volume and tumor bulk/total tumor volume on *T2-FLAIR* images. Hu et al (82) collected 81 tissue samples using a neuro-navigation biopsy procedure from 18 GBM patients and investigated the differences between gene mutations in the enhancing tumor and brain around tumor based on multi-parametric MRI. *PDGFR-α* amplification was strongly linked to the texture feature belonging to discrete orthonormal Stockwell transform (*DOST*) and gray-level co-occurrence matrix (*GLCM*) categories, derived from isotropic diffusion maps (*p*), and moderately correlated to *DOST* texture on *EPI+C* images.

Vascular Endothelial Growth Factor (VEGF)

In glioblastoma, neo-angiogenesis is a crucial physiologic process to ensure existence of an adequate blood supply for proliferation, survival, and invasion of tumor cells. The *VEGF* and its receptor (*VEGFR*), which belong to the *PDGF* supergene family, is among the dominant pro-angiogenic factors regulating angiogenesis in gliomas. *VEGF* expression in glioblastoma occurs mostly in the vicinity of necrotic and hypoxic regions through hypoxia-dependent and –independent mechanisms. Hypoxia is observed in the regions deprived of oxygen, leading to accumulation of hypoxia inducible factor-1α (HIF-1α) which activates several hypoxia-related genes, including *VEGF*. Hypoxia-independent mechanism of *VEGF* upregulation acts through dysregulated activation of mitogenic and survival pathways (83–85). Several anti-angiogenic drugs and therapies for inhibition of *VEGF(R)* have been developed and are undergoing clinical trials or approved (bevacizumab, as an anti–*VEGF-A* humanized monoclonal antibody) for treatment of glioblastoma. However, these drugs have shown no benefit for improving the overall survival (86).

In a preliminary study, Diehn et al (29) showed that contrast enhancement was associated with the activation of tumor hypoxia genes (including *VEGF*). Beig et al (87,88) performed RNA sequencing for 21 gene expression profile which are associated with hypoxia. Three clusters of low, medium, and high hypoxia index were identified to be correlated with radiomic features. Texture features that quantify structural heterogeneity within edema region on *T1w* and *T2w* images, and features that represent the edges and ripples in the

enhancing tumor region on *T2-FLAIR* images were significantly associated with the hypoxia enrichment score.

With a different perspective about the connection between fractal features of volumetric contrast enhancement regions on *T1CE* and tumor genomics, Miller et al (89) calculated fractal pattern features from 39 GBMs. They showed significant correlations of high fractal dimension with mitochondrial respiration/ATP production pathways and increased *VEGF* expression. They concluded that the complexity of contrast enhancement represented by variations in fractal features is linked to the genetic pathways of a shift to glycolytic metabolism and *VEGF* expression.

Epidermal Growth Factor Receptor (EGFR)

EGFR is a cell surface protein and a transmembrane tyrosine kinase receptor, present in epidermal cells, and is a key factor in regulating cell division and death. *EGFR* gene encodes the *EGFR* protein to extend the membrane for one end to remain inside and the other to project outside. This allows the protein to attach to ligands for receiving signals helpful for the cell to respond to the environment (90), which follows by activation of a series of intracellular signaling cascades influencing apoptosis, angiogenesis, and invasion.

Overexpression or amplification of *EGFR* gene is a feature of more aggressive primary glioblastoma (approximately 60%) and is less frequent in secondary glioblastoma (~10%) (91). The most common mutant of *EGFR* is called variant three (*EGFRΔIII*, or *EGFRvIII*), which results from deletion of exons 2 to 7 of the *EGFR* gene. This mutation has been suggested to be crucial in gliomagenesis and causes increased proliferation, motility, aggressiveness and resistance to therapy for tumor cells (92,93).

Targeting *EGFR* has shown satisfactory outcomes for several cancers such as colorectal cancer, non-small cell lung cancer, and pancreatic cancer. While being a ‘signature molecule’ for glioblastoma, the reason behind unsuccessful application of *EGFR* targeting drugs is still undetermined. It is suggested that the failure of *EGFR*-targeting therapies is attributed to drug delivery issues, numerous adaptive mechanisms, alternate pathway adaptation and less relevance in later stages of the disease (94,95).

EGFR amplification/overexpression occurs mostly in the infiltrating edges and is a factor for upregulating the genes that play a role in glioblastoma invasiveness (96,97). Thus, from an MRI standpoint, the infiltrating tumor sub-regions, especially in the edema, seem to harbor relevant radiographic signatures to *EGFR* amplification/overexpression. In 2005, Aghi et al (98) examined 75 patients with glioblastoma and found an increased value for *T2* (high intensity) to *T1* enhancement ratio, and fuzzier borders for tumors with *EGFR* amplification. This alteration can produce peritumoral edematous/tumor-infiltrated tissue and angiogenesis, facilitating tumor invasion into the surrounding tissue. This can be further explained by the less sharpness of tumor borders indicating an indefinite border between active tumor and the peritumoral edematous/tumor-infiltrated tissue. In consistency, Bosnyak et al (99) suggested a lower *T1* contrast volume and lower *T1/T2* volume for tumors with *EGFR* amplification. Diehn et al (29) showed that *EGFR* overexpression is significantly associated with higher ratio of CE volume to necrotic core volume. Conversely, Gutman et al (81) found that the

necrosis/CE ratio was significantly higher in *EGFR* mutants. In a research by Bale et al (100), higher diffusion restriction was observed in tumors with *EGFR* amplification while lesion enhancement was not specific for *EGFR* amplification.

EGFR alterations are linked to changes in neo-angiogenesis and can be captured by MR perfusion-derived parameters. Arevalo-Perez et al (101) tested 82 glioblastoma tumors with known status of *EGFRvIII* using DCE-MRI, and concluded that patients with *EGFRvIII* mutations showed increased relative plasma volume and K^{trans}. Gupta et al (102) indicated that glioblastoma with *EGFR* amplification had higher *rCBV* and lower *PSR*, and those with *EGFRvIII* mutation had higher median *rPH* than the wildtypes.

Intra-tumoral spatial variation of the *EGFR* mutation has been explored in a few studies. Analysis of biopsy samples collected intra-operatively from CE tumor and NE tumor regions by Hu et al (82) demonstrated that *EGFR* amplification is more prevalent in the CE tumor compared to the NE regions and it significantly correlates with texture features on *rCBV* maps (indicative of microvessel volume and angiogenesis) and a few features based on *T2w* images (reflective of tissue water and edema). Bakas et al (103) proposed a peritumoral heterogeneity index derived from DSC-MRI to characterize peritumoral infiltration and vascularization patterns in the close and distant regions to the CE tumor, and showed that this index serves as a non-invasive imaging signature for predicting *EGFRvIII* status.

In a machine learning approach and using multi-parametric MR images, Akbari et al (104) discovered that *EGFRvIII* mutant group exhibit higher *rCBV* and *PH* scores associated with elevated neo-angiogenesis, lower water concentration based on *T2-FLAIR*, and lower *ADC* value related to dense and non-necrotic regions. Furthermore, they found that *EGFRvIII* mutants occur more frequently in the frontal and parietal lobes while the wildtype tumors are mostly located in the temporal lobe (Fig. 2). This finding was earlier reported by Bilello et al (105), who found that *EGFRvIII* mutations are more prominent in the frontal lobe as compared to the wildtype tumors, which prevail in the right frontotemporal region. However, other findings about location of tumors with *EGFR* amplification or *EGFRvIII* mutation are contradictory with the aforementioned studies. For example, Ellingson et al (56) showed that tumors with *EGFR* amplification or *EGFRvIII* mutation occur most frequently in the left temporal lobe.

Phosphate and Tensin Homolog (PTEN)

PTEN is a tumor suppressor gene that maps to the chromosomal region 10q23 and regulates cell division to avoid uncontrolled or rapid proliferation. It inhibits the growth factor signals from passing through the *PI3K/AKT* signaling pathway. The encoded *PTEN* enzyme makes modifications to other proteins and lipids for removing phosphate groups. Furthermore, it triggers apoptosis process, plays a role in cell migration, adhesion of cells to surrounding tissue, angiogenesis, and possibly helps in maintaining the genetic information of the cell. The aforementioned processes lead to the inhibition of excessive cell growth and tumor formation (90). In most of the cancers, *PTEN* loss or downregulation is one of the most frequent mutations and has been suggested to be an early phenomenon in glioblastomas (106). Some studies suggest that the *PTEN* mutation is linked to poor survival in patients

with glioblastoma (107,108). *PTEN* loss is a rare incident in lower grade tumors, rather, it is a sign of tumor progression into a more malignant form (108).

So far, *PTEN* has not been considered a therapeutic target individually. Early studies on anti-proliferation therapy drugs suggested that *EGFRvIII*-mutant glioblastoma responds to *EGFR* inhibitors when their *PTEN* was intact (109). Only recently, researchers have found a mechanism of resistance to therapies, i.e. ionizing radiation and chemotherapy, which is moderated by phosphorylation of *PTEN* on tyrosine 240 (pY240) by *FGFR* (110). Blocking Y240 phosphorylation in glioblastoma models in mice showed to induce radiation sensitivity and increase survival.

Most of the few studies investigating imaging-*PTEN* mutation have been unsuccessful in indicating any radio-phenotype that can discriminate the glioblastoma with the *PTEN* mutation from the wildtype group (41,111,112). The only study with notable results seems to be the one carried out by Hu et al (82), where in a multi-parametric MRI study of 81 tissue samples, collected by a neuro-navigation biopsy procedure from 18 GBM patients, strong correlation between *PTEN* loss and a texture category called local binary patterns (LBP) on *T2w* images was shown. Furthermore, it was suggested that the loss or deletion of *PTEN* was more common in the CE tumor tissue samples compared to brain around tumor (or the NE tumor component).

The tumors with a lack of loss of *PTEN* (*PTEN* wildtypes) have been reported to occur most frequently in the left frontal lobe and the tumors with *PTEN* loss had a high likelihood of appearing in periventricular white matter regions near the posterior aspect of the left lateral ventricle (56), although this has not been confirmed by other researchers (59).

Signaling Pathways

The alterations such as deletions, amplifications or other mutations in glioblastoma impact genes that function in certain signaling pathways that control the oncogenesis processes and orient the mutations within wider signaling networks that further support the progression of cancer (48). Description of all signaling molecules and pathways involved in glioblastoma is out of scope of this paper. However, it is worthwhile to mention that the most frequently altered signaling pathways in glioblastomas are *RTK/PTEN/PI3K* (signal transduction), *p53* (stress response), and *Rb1* (cell cycle control) pathways (109,113).

Different signaling pathways have been tested against imaging traits. Liu et al (114) identified an angiogenic subgroup of glioblastoma, in which pathways associated with angiogenesis and hypoxia are activated. These patients showed a significantly longer survival when treated with anti-angiogenic therapies, suggesting a benefit of this targeted therapy for this patient subgroup. It has been suggested that radiologically-identified habitats (from a combination of low/high signal intensities on *T1w*/*T1CE*/*T2*w/*T2-FLAIR* images) could relate to pathways and cellular processes such as phosphorylation of *STAT-1* and natural killer cell activity (115). The features quantifying the presence of edges, spots, and ripples (Law energy features) from the CE tumor component showed the best performance for predicting the response of glioblastomas to chemo-RT treatment and were significantly

associated with *PI3K/AKT/mTOR* and apoptosis signaling pathways. The former pathway is involved in cell proliferation and survival, and the latter with cell death (116).

Molecular Subtypes

Gene expression profiling has revealed a convergence of the subtypes of glioblastoma into four expression-based molecular categories, namely classical, neural, proneural, and mesenchymal subtypes with somatic alterations (35). *PDGFRA* amplifications and *IDH1* and *TP53* mutations were most frequently found in the proneural group, *EGFR* alterations were mostly present in the classical group, and *NF1* abnormalities were mainly categorized with mesenchymal GBM (35). These glioblastoma subtypes respond differently to aggressive therapies and the survival benefit of the patient from these therapies varies based on these molecular classes. The mesenchymal and classical subtypes benefit the most from the aforementioned therapies than the proneural group.

Radiogenomic studies have shown differences in the imaging features among different molecular glioblastoma subtypes and have supported the hypothesis of specific phenotypic appearance of each subtype on MRI. Volume of CE tumor, volume of central necrosis, combined volume of CE and central necrosis, and the ratio of *T2-FLAIR* to CE and necrosis were demonstrated to be significantly different in mesenchymal subtype of glioblastoma, as compared to non-mesenchymal subtypes. The best predictor of mesenchymal subtype has been indicated to be low volume ratio of *T2* hyperintensity to contrast enhancement and central necrosis (117). Proneural glioblastomas seem to appear with a significantly lower level of CE (111,118). The mesenchymal subtype indicates lower level of non-enhanced tumor compared to other subtypes (111). This finding has further been supported in other studies that report the mesenchymal subtype to be significantly correlated with minimum intensity in the edema region, the classic subtype to be associated with edge sharpness and intensity within necrosis and peritumoral edematous/tumor-infiltrated regions, in the classical tumors compared to mesenchymal subtype, lower intensity in the edematous/tumor-infiltrated region has been observed (119). Accordingly, features of edge complexity have shown to significantly differentiate between mesenchymal and classical molecular subtypes (120). The edematous/tumor-infiltrated volume and total tumor volume have been suggested as the best predictors of glioblastoma molecular subtypes (40).

None of the $rCBV_{mean}$ or $rCBV_{max}$ parameters calculated from DSC-MR images within the contrast-enhanced part of the lesion were correlated with the molecular subtypes. However, the combination of molecular classification with $rCBV_{mean}$ could be highly predictive of the patient's overall survival (121). The added value of *rCBV* in the NE region ($rCBV_{NER}$) of the tumor to morphologic, clinical, and genomic markers for predicting the overall survival has been sought and shown to increase the predictive performance (122).

CONSIDERATIONS AND CHALLENGES OF RADIOGENOMIC STUDIES

Radiogenomic studies intend to contribute to overcoming the current issue of tissue sampling error, as they can radiographically assess the whole tumor extent. Nevertheless, there are multiple challenges that the scientific community should be taking into

consideration, in order to lead to more repeatable, clinically relevant, and hence more impactful results.

Need for Ample and Diverse Data

Ample and, importantly, diverse data are required to allow identification of robust radio-phenotypic patterns of specific molecular characteristics and produce generalizable biomarkers. Undeniably this need becomes more apparent with the advent of deep learning methodologies, which need a vast amount of data to learn meaningful patterns. Such big numbers and diversity cannot be found within a single institution and, currently, can only be found in retrospective datasets pooled across multiple institutions. There are a few public multi-institutional imaging datasets available via The Cancer Imaging Archive (TCIA, www.cancerimagingarchive.net) (123) that describe primarily data of standard clinical practice, as well as some clinical trial data, with corresponding molecular characterizations available in the National Cancer Institute's Genomic Data Commons portal (NCI GDC, https://portal.gdc.cancer.gov/), as well as corresponding comprehensive proteomic data in the Clinical Proteomic Tumor Analysis Consortium (CPTAC, proteomics.cancer.gov) (124). Results of various existing studies have been made available through the "Analysis Results" dashboard of TCIA website (https://wiki.cancerimagingarchive.net/display/DOI/TCIA+Analysis+Results), enabling future studies to avoid repetition of the efforts and allow reproducibility. An example of such publicly-available results is the expert annotations of glioblastoma sub-regions (125), which have formed the ground truth for the data of the TCGA-GBM (126) and TCGA-LGG (127) collections included in the International brain tumor segmentation (BraTS) challenge (125,128). However, data of standard clinical practice are typically heterogeneous in their acquisition protocol (in terms of both the type of modalities used and their resolution), as well as in the course of treatment followed, which make the data size smaller after inclusion criteria and appropriate curation applies. On the other hand, imaging data from clinical trials follow a standardized acquisition protocol (129), albeit more difficult to be shared publicly due to data-ownership concerns.

Data Processing and Radiographic Feature Extraction

Various data processing routines and varying parameterization of computational methods add to the challenge of identifying ample and diverse data, as further sources of variation in quantitative analyses. In favor of reproducibility, appropriate comprehensive description of the methodological approaches used in radiogenomic studies, and their parameterization, should be at least documented if not distributed as open source implementations. This has been the primary aim of the international multi-institutional effort described by the Image Biomarker Standardization Initiative (IBSI) (130). IBSI attempts to appropriately summarize the mathematical formulation of such computational parameters (e.g., texture features), as well as document the minimum acceptable parameters that should be reported when such parameters are used in scientific studies, while accounting for the input modality.

The overarching goal of such methodological approaches is to extract comprehensive sets of computational parameters (i.e., radiographic features) capturing both visual and sub-visual cues of the underlying tissue structure and reflecting biological pathophysiology. The two main categories of features that are typically considered are based either on conventional

radiomics or deep learning. Conventional radiomics have been primarily described by IBSI (130). The underlying principle of deep learning-based features is to learn patterns from large datasets and utilize them, for example, 1) as attention maps (131,132) to adjust the classifier weights on particular image regions, 2) as additional input modalities, and 3) through transfer learning (133).

We note that numerous radiogenomic studies have been implementing well-known parameters for their individual studies. In favor of reproducibility, multiple open-source software toolkits have been developed and made available, facilitating the extraction of various quantitative image characteristics and offering the potential for harmonized processing pipelines. Example of such software tools include, but are not limited to, 3D Slicer (www.slicer.org) (134), PyRadiomics (www.radiomics.io/pyradiomics.html) (135), and the Cancer Image Phenomics Toolkit (CaPTk, www.cbica.upenn.edu/captk) (136).

Curse of Dimensionality

It is commonly observed that the number of radiographic features can be significantly larger than the number of subjects involved in a study. This is expected to lead to a well-known issue in the domain of machine learning, overfitting the data used to train a machine-learning-based biomarker, therefore resulting to non-generalizable results. This is not to say that the extraction of radiographic features should be limited, as the more comprehensive the panel of extracted radiographic features, the more comprehensive the characterization of the region of interest. Nevertheless, this “curse of dimensionality” raises the need for appropriate cross-validation and feature selection methods. Cross-validation is a well-established way to provide unbiased performance estimates of a biomarker, quantitatively validate its generalization performance, and enable analysis of a given dataset as if independent retrospective and prospective cohorts existed, but in a more statistically robust manner by randomly permuting across the provided dataset (137). Feature selection results in ranking a large number of extracted features based on their descriptive/predictive power on the given dataset, while they account for feature collinearities and therefore redundancies.

FUTURE DIRECTIONS

Most radiogenomic studies have focused on predicting individual molecular characteristics from pre-operative baseline scans. Taking into consideration that the concept of *precision medicine* is defined by precise molecular tumor characterization, these studies may be considered redundant for actual patient management primarily for two reasons. First, in many cancers, we note disruptions of multiple pathways (therefore associative multi-mutational status) for a single patient, instead of an individual molecular characteristic. Second, such radiogenomic studies revolve around precision medicine, whereas in most situations precise tumor characterization will occur anyway, histopathologically, after radiographically identifying a brain tumor suspected of being a glioblastoma.

On the other hand, it has become apparent that glioblastoma molecular characteristics show spatiotemporal heterogeneity, described by either loss of mutant expression at the time of progression (138) or after treatment, both following standard chemo-radiation (139) and

peptide vaccination (140) creating an even further complicated picture (141). This is where radiogenomic studies could contribute.

Taking all the above into consideration, there is a need for future directions of radiogenomic studies focusing on the concept of *personalized/adaptive medicine*, instead of revolving around precision medicine. This would allow to potentially determine if baseline (developed in the primary tumor) radio-phenotypes are preserved in follow up scans irrespective of treatment, thereby recognizing the historic molecular profiling of recurrent tumors, or if there are radio-phenotypical variations over time that would allow the non-invasive longitudinal monitoring of mutational status, thereby evaluating treatment response.

Exemplar computational studies have shown promise on training machine-learning-based models across multiple institutions without sharing patient data (142,143). Such distributed learning approaches could be investigated further in radiogenomic studies, thereby addressing the issue of identifying ample and diverse datasets while also overcoming the various data-ownership concerns, and facilitating the exploitation of the full potential of homogenized clinical trial data.

Finally, the bi-disciplinary radiogenomic studies started to expand naturally towards synergistic analyses of radiographic, histopathologic, genetic, and clinical information. Such radio-patho-genomic analyses should speed up scientific discovery and lead to quantitative integrated evaluations of patient data on multiple scales, with the intention of contributing towards improving personalized and precision medicine. These integrated diagnostic approaches could contribute on the specificity of radio-phenotypes associated to distinct molecular signatures, that current radiogenomic studies have proved only for 2HG MRS (64).

CONCLUSION

Radio-phenotypical (MRI) signatures can assist in tackling the spatiotemporal heterogeneity concern, as well as in detecting properties relating to tumor structure, perfusion/neo-angiogenesis, cellular distribution/density, and metabolic processes. Mounting ongoing research, investigating the connections between radiographic signatures and underlying genetic changes in glioblastoma, have supported the idea that these alterations are followed by radio-phenotypic manifestations. However, current findings are substantially divergent. The reason lies in a) inter-patient heterogeneity of glioblastoma, b) the lack of large cohorts that can represent this heterogeneity, and c) missing standardized multi-institutional guidelines for systematic image acquisition and analysis. With maturation of radiogenomic studies through incorporation of machine-learning methods for systematic and reproducible methods, there is a hope to find specific radio-phenotypic models that reveal the Achilles heel of glioblastoma and encourage personalized targeted therapies.

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ABBREVIATIONS

2HG	2-hydroxy-glutarate
ADC	Apparent Diffusion Coefficient
ASL	Arterial Spin Labeling
(r)CBF	(Regional or Relative) Cerebral Blood Flow
(r)CBV	(Regional or Relative) Cerebral Blood Volume
CE	Contrast-Enhancing Tumor
Cho	Choline metabolite
CNS	Central nervous system
Cr	Creatine metabolite
DCE-MRI	Dynamic Contrast-Enhanced MRI
DNA	Deoxyribonucleic Acid
DSC-MRI	Dynamic Susceptibility-weighted Contrast-enhanced MRI
DTI	Diffusion Tensor Imaging
DWI	Diffusion Weighted Imaging
EGF(R)	Epidermal Growth Factor (Receptor)
EPI (+C)	Echo-Planar Imaging (+Contrast)
FA	Fractional Anisotropy
FGFR	Fibroblast Growth Factor Receptor
FLAIR	Fluid Attenuated Inversion Recovery
GBM	Glioblastoma (formerly known as Glioblastoma Multiforme)
Glx	Glutamate and Glutamine metabolite
HIF1A	Hypoxia Inducible Factor 1 Subunit Alpha
IDH	Isocitrate DeHydrogenase
K_{ep}	flux rate constant
K^{trans}	The volume transfer constant
MD	Mean Diffusivity
MGMT	O^6 Methylguanine-DNA Methyltransferase

miRNA	microRNA
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
NAA	N-acetylaspartate metabolite
NE	Non-enhancing Tumor
NF1	Neurofibromin 1
NGS	Next Generation Sequencing
PDGF(R)	Platelet-Derived Growth Factor (Receptor)
POSTN	Periostin gene
PH	Peak Height
PI3K	Phosphoinositide 3-kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-Kinase Catalytic subunit Alpha
PSR	Percentage of Signal Recovery
PTEN	Phosphatase and Tensin homolog
RNA	Ribonucleic Acid
RTK	Receptor Tyrosine Kinases
SVZ	Subventricular Zone
T1CE	Contrast-Enhanced T1-weighted MRI
T1w	T1-weighted MRI
T2w	T2-weighted MRI
TERT	Telomerase Reverse Transcriptase
TP53 (or p53)	Tumor protein p53
V_e	extracellular volume ratio
VEGF(R)	Vascular Endothelial Growth Factor (Receptor)
VS	Vessel Size
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
WHO	World Health Organization

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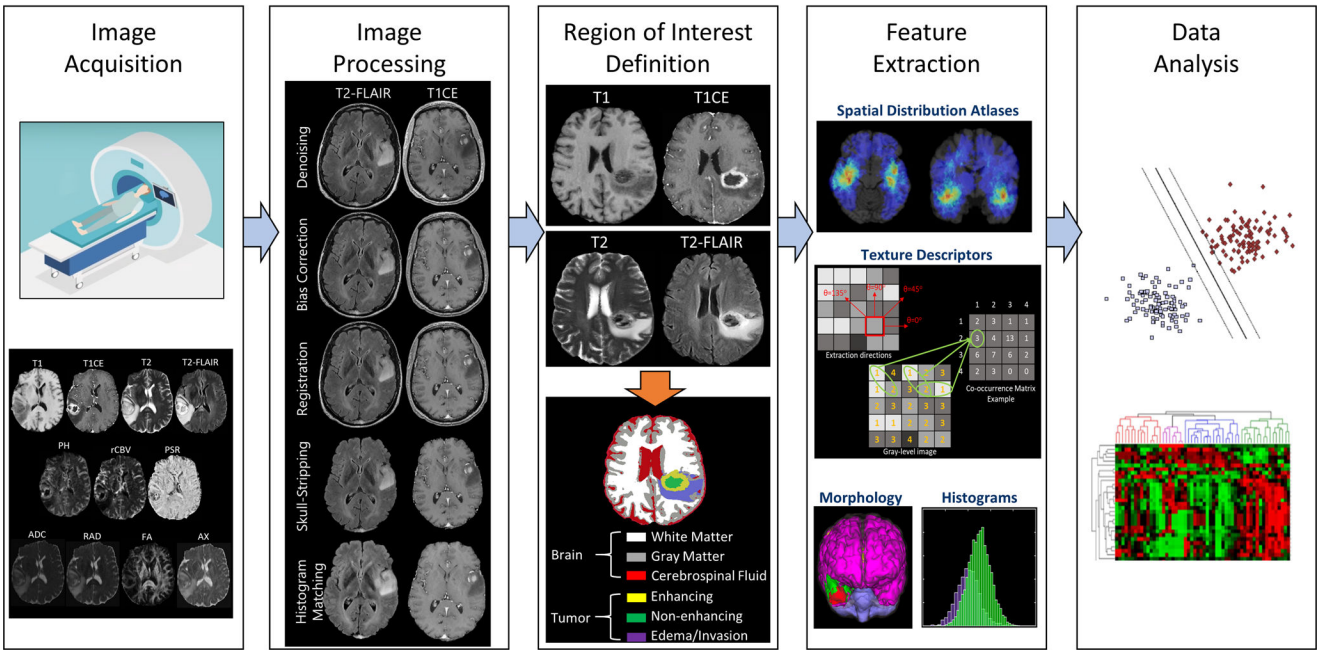

Fig. 1.

A representation of the proper workflow of a radiomic study, which includes the following steps: 1) image acquisition, 2) image processing, including noise/artifact reduction, intensity and/or orientation standardization, co-registration of the multi-parametric MRI scans, 3) region-of-interest definition using manual annotation or (semi-)automatic segmentation, 4) feature extraction based on human-engineered (conventional radiomics) or deep learning approaches, and 5) data analysis, involving machine/deep learning methods for feature selection, classification, and cross-validation. Radiogenomics studies should ideally follow the same workflow, with genomics of glioblastoma as their endpoint.

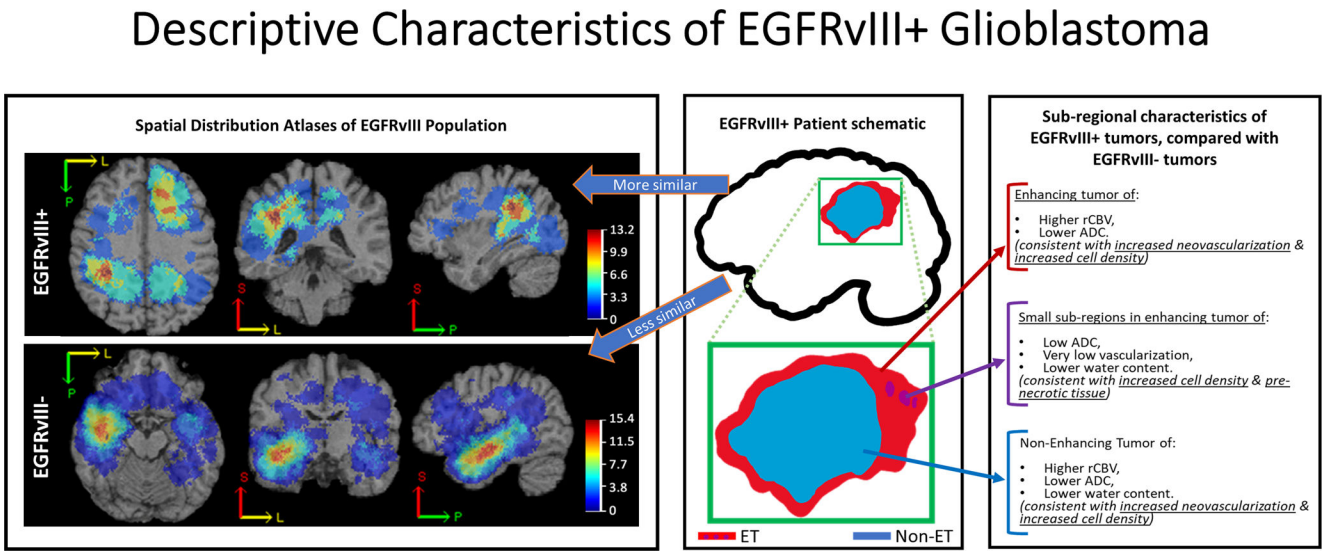

Fig. 2.

An illustration of descriptive characteristics of mutant EGFRvIII (EGFRvIII+) tumors (adopted from ref. (104) with permission from the authors and the publisher (Oxford University Press, License No. 4636511399697)).

Table 1.

A summary of radiogenomic studies that have undertaken the systematic workflow (according to Fig.1)

Study	MRI Techniques	Molecular Characteristic(s)	The number of Patients in the Cohort
Itakura et al, 2015 (33)	T1CE	Multiple signaling pathways	n=265 (development cohort (n=121), validation cohort (n=144))
Kickingereder et al, 2016 (112)	T1w, T1CE, T2w, T2-FLAIR, DWI, DSC-MRI	Molecular subtypes (mesenchymal, RTK 1 “PDGFRA”, RTK II “classic”, IDH1, G34) and multiple genes (MGMT, EGFR, PDGFRA, MDM4, CDK4, PTEN, CDKN2A, NF1, Rb1)	n=152
Korfiatis et al, 2016 (72)	T1w, T1CE, T2w	MGMT methylation	n=155
Macyszyn et al, 2016 (118)	T1w, T1CE, T2w, T2-FLAIR, DTI, DSC-MRI	Verhaak’s Molecular Subtypes	n=99
Kickingereder et al, 2017 (74)	T1w, T1CE, T2-FLAIR	MGMT methylation	n=181 (discovery set (n=120), validation set (n = 61))
Li et al, 2018 (73)	T1w, T1CE, T2w, T2-FLAIR	MGMT methylation	n=193 (primary cohort (n=133), validation cohort (n=60))
Beig et al, 2017 (87)	T1CE, T2w, T2-FLAIR	Hypoxia pathways	n=115 (training set (n=85), independent validation set (n=30))
Bakas et al, 2018 (103)	DSC-MRI	EGFRvIII	n=142 (discovery cohort (n=64) and replication cohort (n=78))
Akbari et al, 2018 (104)	T1w, T1CE, T2w, T2-FLAIR, DTI, DSC-MRI	EGFRvIII	n=129 (discovery cohort (n=75) and replication cohort (n=54))
Rathore et al, 2018 (34)	T1w, T1CE, T2w, T2-FLAIR, DTI, DSC-MRI	Verhaak’s Molecular Subtypes	n=261 (discovery cohort (n=208), validation cohort (n=53))
Chang et al, 2018 (52)	T1w, T1CE, T2w, T2-FLAIR	IDH1, MGMT, 1p/19q co-deletion	n=259

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Table 2.

Summary of MRI phenotypes that have more repeatedly been reported in radiogenomics studies to be associated with specific molecular signature(s)

Molecular Signature(s)	MRI Phenotype	Radiogenomic Studies
IDH1 mutation		
	Large proportion of non-enhancing tumor compared to tumor enhancement	(52), (54)
	Higher CBF, large necrosis	(55)
	Frontal location of tumor	(53,56,57,59)
	Concentration of 2HG metabolite	(60–63)
MGMT Promoter Methylation		
	Higher K^{trans}	(70)
	Higher minimum ADC	(71)
	Higher proportion of non-enhancing tumor	(52)
	Left temporal lobe location of tumor	(56,76)
VEGF mutation		
	Contrast enhancement	(29)
	Heterogeneous edema	(87,88)
EGFR amplification of EGFRvIII mutation		
	Higher ratio of the volume of T2w to T1CE abnormality	(98,99)
	Higher diffusion restriction	(100,104)
	Elevated K^{trans}, rCBV, PH	(82,101–104)
Molecular Subtypes		
Mesenchymal subtype	Lower ratio of the volume of T2w to T1CE abnormality	(111,117,119)
Proneural subtype	Lower contrast enhancement	(111,118)
Classic subtype	Lower intensity in the edema region	(119)