Radiogenomics of Gliomas

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KEYWORDS

- Radiogenomics • Radiomics • Gliomagenesis
- Visually accessible rembrandt imaging (VASARI) feature set • The cancer genome atlas (TCGA)
- Isocitrate dehydrogenase (IDH) • 1p/19q codeletion
- Epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF)

KEY POINTS

- Current research in brain tumors is focused on tumor genomics to identify novel therapeutic targets, devise personalized treatment options, and thereby improve individual patient outcomes.
- Radiogenomics is the study of relationship between imaging features (radiophenotypes) and genetic/molecular profile of disease state, typically neoplasms.
- Primary de novo tumors account for more than 80% of glioblastomas (GBs), occur in older patients, and typically show epidermal growth factor receptor gene amplification and mutation, loss of heterozygosity (LOH) of chromosome 10q containing phosphatase and tensin (PTEN) homolog, deletion of p16, and less frequently murine double minute 2 (MDM2) amplification.
- Secondary GBs develop from lower-grade astrocytomas or oligodendrogliomas, occur in younger patients, and often include mutations of TP53, retinoblastoma, and LOH of chromosome 19q.
- The radiomic features derived from clinical sequences, such as T2, fluid-attenuated inversion recovery (FLAIR), T1, and T1 with contrast, as well as from advanced imaging techniques, such as diffusion, perfusion, and diffusion tensor imaging, can give a detailed overview of the local and global genomic heterogeneity of the tumor environment.

INTRODUCTION

The 2003 Human Genome Project and the 2016 World Health Organization (WHO) classification have made significant impact on understanding of brain tumors.[1,2] Current brain tumor classification is based on genomic and molecular profile of tumor tissue, and these characteristics play an important role in treatment planning and prognostication. Current research in brain tumors is focused on tumor genomics to identify novel therapeutic targets, devise personalized treatment options, and thereby improve individual patient outcomes.[3] In parallel, MR imaging of brain tumors also has seen rapid growth, with development of advanced imaging techniques that provide insight into tissue characteristics at cellular and molecular levels. MR image processing and analysis have

made remarkable progress, with development of niche areas of texture analysis/radiomics and applications of machine learning techniques and artificial intelligence.[4] Because MR imaging offers a unique noninvasive way of comprehensively evaluating tumor milieu, it is no surprise that a new field of radiogenomics has made significant strides in merging imaging with genomic mapping. One of the earliest initiatives to encourage interest in this area was The Cancer Genome Atlas (TCGA) program, which was a joint effort between the National Cancer Institute and the National Human Genome Research Institute. The Cancer Imaging Program has made radiological imaging data for glioblastoma (GB) patients enrolled in TCGA publicly available via the Cancer Imaging Archive (TCIA).[5] This large-scale effort has paved the way for numerous impactful studies exploring potential

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correlations between tumor imaging features, histologic patterns, and genetic profiles and firmly established the field of radiogenomics.

OVERVIEW OF GLIOMA BIOLOGY

Human gliomas can be classified into low-grade gliomas (LGGs) and high-grade gliomas based on their histopathology.[2] LGGs are treated with maximal safe resection and eventual reoperation with adjuvant radiation and/or chemotherapy, and typically have a life expectancy of 10 years to 15 years after diagnosis.[6] High-grade gliomas comprise anaplastic astrocytomas (grade III) and GBs (grade IV). Treatment of GB remains a challenge, with median overall survival of 14 months despite aggressive therapy. The GB treatment regimen consists of a combination of maximally safe surgical resection followed by radiation therapy and concurrent chemotherapy.[7] Tumor heterogeneity, one of the hallmarks of GB, is the presence of multiple different cell subpopulations within a single tumor. It is caused by cancer stem cells that possess varying degrees of ability to self-renew and differentiate into different tumor cell types and also the ability for clonal evolution that may enhance genetic diversity within the affected tissues. Because tumor fragments from the same patient may have different molecular subtypes in different tumor regions, GB grading can be complex. GBs also show epithelial to mesenchymal transitions, thought to be due to signaling pathways of Wnt, transforming growth factor β, and NOTCH. This transition is partly responsible for the migration, diffusion invasion, and angiogenesis of GB. By virtue of the inherent heterogeneity of these tumors, not all of the cells within a glioma respond to chemotherapy and radiation equally and effectively, resulting in tumor progression/recurrence.[8]

Gliomagenesis is a multifactorial process involving more than 60 genetic alterations. Primary de novo tumors accounts for more than 80% of GBs, occur in older patients and typically show epidermal growth factor receptor (EGFR) gene amplification and mutation, loss of heterozygosity (LOH) of chromosome 10q containing phosphatase and tensin homolog (PTEN), and deletion of p16, and less frequently murine double minute 2 (MDM2) amplification. Secondary GBs develop from lower-grade astrocytomas or oligodendrogliomas, occur in younger patients, and often include mutations of TP53, retinoblastoma (RB), and LOH of chromosome 19q.[9] Because it is well-established that treatment response and overall survival depend on the molecular and genomic characteristics, identifying the radiogenomic links becomes vitally important for the radiologist and the oncologist.

DEFINITIONS AND TERMINOLOGY

Radiogenomics is the study of relationship between imaging features (radiophenotypes) and genetic/molecular profile of disease state, typically neoplasms. In a broader sense, radiogenomics also may encompass study of genomic changes induced by radiation therapy, but a more focused definition used commonly by cancer imaging community refers to the earlier description alone.[10] The radiophenotypes used for radiogenomics can be derived from conventional clinical imaging data or from advanced imaging techniques, such as permeability imaging, perfusion imaging, diffusion tensor imaging (DTI), and MR spectroscopy. The radiophenotypes can be radiologist derived, also known as semantic, and harvested with minimal data processing, or they can be computer-derived radiomic parameters, which quantitatively measure texture features that are not visible to human eye. The genomic profile of tumors can be determined by analysis of DNA, RNA, or protein, with emphasis on presence, absence, overexpression, or suppression of these markers. The commonly used techniques can identify targeted gene mutations or their downstream effects or provide whole-genome sequencing.

MOLECULAR CHARACTERISTICS OF GLIOMAS

The 2016 WHO classification of brain tumors outlined specific molecular parameters for diagnosis of brain tumors in combination with the more traditionally used histologic features.[2] This has significantly altered the overall clinical approach to diagnosis and classification of glioma subtypes.

Isocitrate Dehydrogenase Gene 1/Isocitrate Dehydrogenase Gene 2

Isocitrate dehydrogenase gene (IDH) mutation is one of the key molecular markers described in relation to gliomas. IDH is a key enzyme in the cell citric acid cycle and a mutation in IDH1 or IDH2 gene results in altered enzyme activity with accumulation of 2-hydroxyglutarate (2-HG). Accumulation of 2-HG, in turn, causes a cascade of events that results in DNA hypermethylation to affect cell differentiation and neoplasia. This mutation can be detected in clinical setting by immunohistochemistry and whole-genome sequencing. Detection of IDH1/2 has significant implications for diagnosis and prognosis of gliomas. GBs are classified as primary (wild-type) or secondary (IDH-mutant) based on IDH mutational status.[11]

IDH mutation is also indicative of a diffuse glioma (grade II and grade III) and is useful to distinguish these tumors from reactive gliosis or discrete grade I gliomas, such as pilocytic astrocytoma. Presence of IDH mutation is a favorable prognostic indicator with better overall survival and progression-free survival. More importantly, patients with a LGG (grade II or III) with a wild-type IDH have worse outcomes that are similar to grade IV tumors.[12]

1p/19q Codeletion

1p/19q codeletion was one of the earliest chromosomal abnormalities described in patients with oligodendroglial tumors and is detected in clinical setting using fluorescence in situ hybridization.[13] Only recently has it been shown that the codeleted tumors have key physical and chemical attributes that have an impact on migration, apoptosis, and cell-cycle regulations. Presence of 1p/19q codeletion is indicative of LGGs, supports the diagnosis of an oligodendroglial tumor, and is seen in more than 70% tumors with oligodendroglial origin.[14] Presence of this codeletion is associated strongly with excellent response to chemotherapy with alkylating agents and remains a strong favorable prognostic factor associated with improved survival. A key study based on TCGA database found that LGGs with 1p/19q codeletion and IDH mutations had significantly higher survival (median survival of 8 years) compared with patients with IDH mutations without codeletion (median survival of 6.3 years) and patients with IDH wild-type tumors (median survival of 1.7 years).[15–17] In another study, grade II and grade III gliomas were classified into 5 different subtypes based on IDH, 1p/19q, and telomerase reverse transcriptase (TERT) mutational status with distinct clinical outcomes.[18]

O6-methylguanine-DNA Methyltransferase

O6-methylguanine-DNA methyltransferase (MGMT) is a DNA repair enzyme located on chromosome 10q, and methylation of the promoter region of the gene results in lower levels of this enzyme, resulting in less efficient DNA repair in tumor cells damaged due to cytotoxicity.[19] MGMT methylation status is detected with pyrosequencing or by a quantitative polymerase chain reaction test. It is a positive prognostic factor and is a strong predictor of positive therapeutic response to temozolomide in new and recurrent high-grade gliomas.[20,21] MGMT methylation also frequently is seen in IDH-mutant LGGs and is associated with favorable survival.[22] In patients with GBs treated with standard therapy, the incidence of pseudoprogression is significantly higher in tumors with methylated MGMT.[23]

Epidermal Growth Factor Receptor and Vascular Endothelial Growth Factor

High-grade gliomas are associated with abundant and disorderly cellular and vascular proliferation. Amplification and mutation of the EGFR gene located on chromosome 7q12 induce rapid cellular growth, resulting in an aggressive proliferative neoplasm. EGFR amplification is commonly associated with classical subtype and is seen more frequently in primary GBs compared to secondary GBs. The EGFR mutated cell lines can be suppressed by EGFR inhibitors, such as erlotinib and gefitinib, raising the possibility of targeted therapeutics. Clinically, EGFR abnormalities can be detected by immunohistochemistry or EGFR staining.[24–28] High-grade gliomas also are characterized by overexpression of vascular endothelial growth factor (VEGF), which is responsible for neoangiogenesis.[29] Hypoxia in the tumor microenvironment acts as a stimulus for angiogenesis by activation of hypoxia inducible factor 1 subunit alpha. Other factors that drive hypervascularization such as angiopoietin-1 and angiopoietin-2, hepatocyte growth factor, and platelet-derived growth factor (PDGF) are also activated by hypoxia. The ultimate result of this process is a neoplasm with profuse leaky aberrant vasculature with deficient blood-brain barrier. Bevacizumab is an anti-angiogenic agent that targets VEGF overexpression and often is used in treatment of recurrent GBs.[30]

Other Key Mutations

Other key molecular aberrations and genetic mutations in gliomas include alpha-thalassemia mental retardation (ATRX), TERT, TP53, and neurofibromatosis type 1 (NF1) histone H3 K27M, among several others.[9,31–34] X-linked gene of ATRX mutations affect DNA repair and are found in low-grade astrocytomas. TERT mutations result in intact length of telomeres, which confers the ability to divide ad infinitum. These often are seen in gliomas in combination with ATRX mutations. Based on the findings from TCGA study, the key signaling pathways that drive tumor growth in GBs are the RB pathway, the TP53 pathway, and the PTEN/NF1/RTK (receptor tyrosine kinase) pathway. The RB and TP53 are known tumor suppressor genes, and mutations in this pathway result in increased mitotic activity and suppressed apoptosis, respectively. The PTEN/NF1/RTK pathway abnormalities simultaneously

cause increased cell growth, modulate cell cycle, and affect tumor suppression. Lastly, histone H3 gene mutations cause abnormalities of DNA packing and are seen in pediatric diffuse intrinsic pontine gliomas and pediatric GBs. Recent WHO classification has defined a new entity called diffuse midline glioma with H3 K27M-mutant. Although these tumors demonstrate low grade on histology, they are considered grade IV due to their aggressive behavior.[2]

Transcriptomic Subtypes

Depending on the molecular and genomic characteristics, GBs can be classified into classical, mesenchymal, neural, and proneural. Each subtype is associated with a distinct set of molecular features with distinct clinical behaviors. For example, the proneural subtype is associated with IDH mutations, includes a majority of secondary GBs, and is associated with best prognosis. The mesenchymal type, on the other hand, is associated with increased mutations of PTEN, TP53, and NF1 genes and correlates with poor radiation response and shorter survival. The neural subtype is characterized histologically by higher astrocyte and oligodendroglial differentiation and is highly infiltrated by healthy brain cells.[25,27] Fig. 1 provides an overview of current classification of adult and pediatric gliomas.

APPROACH TO RADIOGENOMIC ANALYSIS

Simply put, a radiogenomic study allows for assessment of relationship between imaging patterns and genomic signatures in disease states, typically cancer. These studies are focused primarily either on identifying the possible molecular associate with the specific radiographic correlate or studying how a particular genomic variation might have an impact on the tumors' imaging characteristics. The first category of studies can be classified as exploratory, whereas the second category of studies can be classified as hypothesis driven. Early radiogenomic literature focused primarily on a single imaging characteristic (for example, presence of necrosis) and correlated the presence or absence of this feature with the corresponding tissue molecular and genomic features. These studies predominantly used semantic features to harvest tumor radiophenotypes (for example, the Visually Accessible Rembrandt Imaging [VASARI] feature set) and incorporated targeted tissue sampling using neuronavigational techniques to sample areas with specific imaging features. Subsequent radiogenomic studies using semantic features explored associations between imaging phenotypes and more targeted genomic characteristics with direct implications for treatment planning and outcome. More recent studies have focused on exploring correlations between
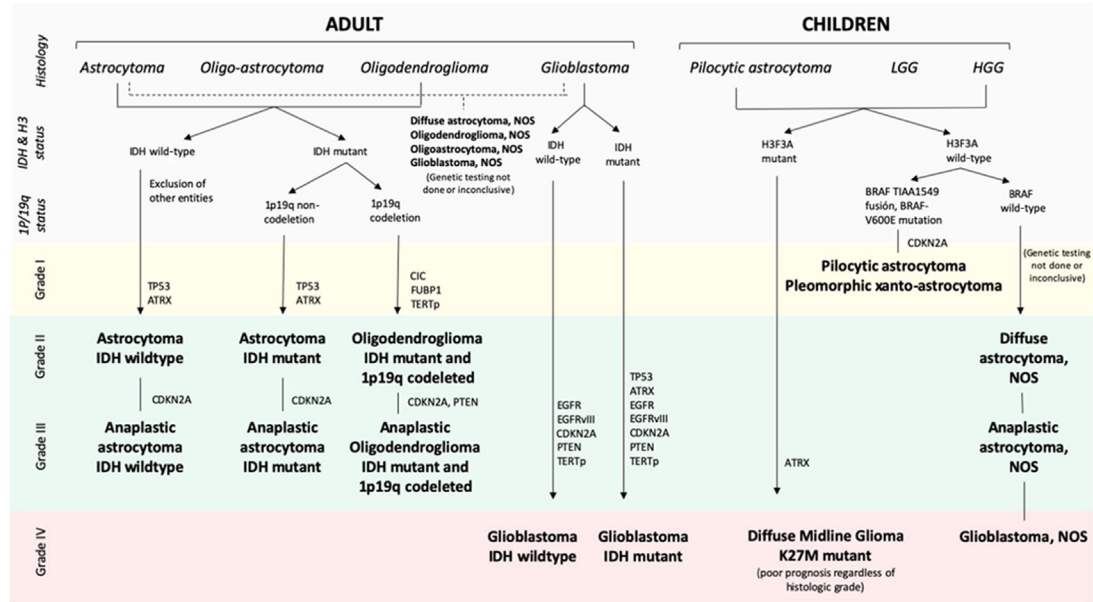

Fig. 1. Schematic classification of adult and pediatric diffuse gliomas according to status of relevant biomarkers. HGG, high grade glioma; NOS, not otherwise specified. (*From* Delgado-López PD, Saiz-López P, Gargini R, Sola-Vendrell E, Tejada S. A comprehensive overview on the molecular biology of human glioma: what the clinician needs to know. Clin Transl Oncol. 2020.)

computer-derived radiomic features and large-scale gene expression patterns. A smaller subset of these studies falls under the category of a directed or hypothesis-driven approach, where more specific gene expression profiles or genetic pathways are targeted for analysis using quantitative metrics derived from conventional and advanced imaging sequences.

RADIOGENOMIC STUDIES USING SEMANTIC FEATURES

TCGA initiative led to the development of the VASARI feature set, which consisted of 24 common MR imaging observations routinely made during clinical interpretations (https://www.cancerimagingarchive.net/). These observations were made using standard contrast-enhanced MR imaging acquisitions and included features, such as location, laterality, proportion and quality of enhancement, proportion of necrosis, cysts, diffusion, and so forth. These feature sets were utilized to create subjective and objective markups of baseline MR imaging–GB studies stored in TCIA for TCGA and linked to the Repository of Molecular Brain Neoplasia Data (REMBRANDT) set.[35] These imaging data sets were utilized mainly to understand the correlation of imaging phenotypes with survival, molecular subtypes, mutation status, and copy number expression. Some of the key VASARI imaging features that have demonstrated correlation with brain tumor genomics are location, tumor volume, edema, and necrosis, enhancing versus nonenhancing areas, and diffusion characteristics. Although perfusion imaging was not included in the VASARI data set, perfusion characteristics of tumor have also emerged as key semantic feature for radiogenomic correlation.

Location and Volume

Tumor volume and location of tumor are shown to be robust imaging phenotypes that have strong correlation with genomic features.[36–42] For tumor volume analysis, fluid-attenuated inversion recovery (FLAIR) and postcontrast T1-weighted images are used most commonly to segment out enhancing tumor volume, nonenhancing tumor volume, and necrosis with manual or automated techniques and then correlated with genomic profile. For studies based on tumor location, features, such as location, laterality, involvement of eloquent cortex, multifocality, periventricular involvement, and extension across midline, have been used to explore genomic correlations. For example, MGMT methylated IDH-mutant tumors are located primarily in the frontal lobe or subventricular region of the frontal horns of the lateral ventricles and are less likely to invade eloquent areas of the brain, whereas amplified and variant EGFR-expressing tumors occurred most frequently in the left temporal lobe.[36,42]

In 2012, Zinn and colleagues[43] studied 78 GB patients from TCIA data set and generated a prognostic model for patient survival based on the volume of enhancing tumor (including the necrotic core), patient age, and Karnofsky performance scale status (VAK). Larger volume tumor, age of 60 years or more, and Karnofsky performance scale status less than 100 were noted and patients with none or only 1 feature were categorized as VAK-A, whereas patients with 2 or all 3 features were categorized as VAK-B. The investigators also identified differences in gene and mRNA expression profile between these 2 groups. They found class VAK-A was associated with P53 activation whereas class VAK-B was associated with P53 inhibition. Adding MGMT-promoter methylation status to VAK-A stratified the data further, such that the MGMT methylated VAK-A cohort was found to have significantly longer survival compared with other 3 groups (**Fig. 2**).[43]

Enhancement Characteristics

Enhancing and nonenhancing components of GB have been extensively studied in relation to gene expression. In one of the earliest efforts, Pope and colleagues[44] compared the imaging findings of 52 GBs with microarray analysis of tissue derived from areas with different enhancement characteristics. They specifically analyzed the gene expression between lesions with complete enhancement and lesions with incomplete ring enhancement and confirmed that interleukin-8 and VEGF gene expression were higher in the former subset compared with the later.[44] Barajas and colleagues[45] also had similar results demonstrating the intertumoral and intratumoral regional differences in genetic and cellular expression patterns. They further confirmed that the contrast enhancing regions had more complex vascular hyperplasia as well as increased hypoxia and tumor cell density and up-regulation of VEGF and various collagen genes.[45]

Peritumoral Edematous/Tumor-Infiltrated Tissue

The nonenhancing T2-FLAIR hyperintensity surrounding the enhancing tumor core often represents a mixture of edema and tumor infiltration, particularly in GBs. This region is of particular interest because it often includes the site of future recurrence, which invariably occurs in GBs. Various studies have explored the radiogenomic
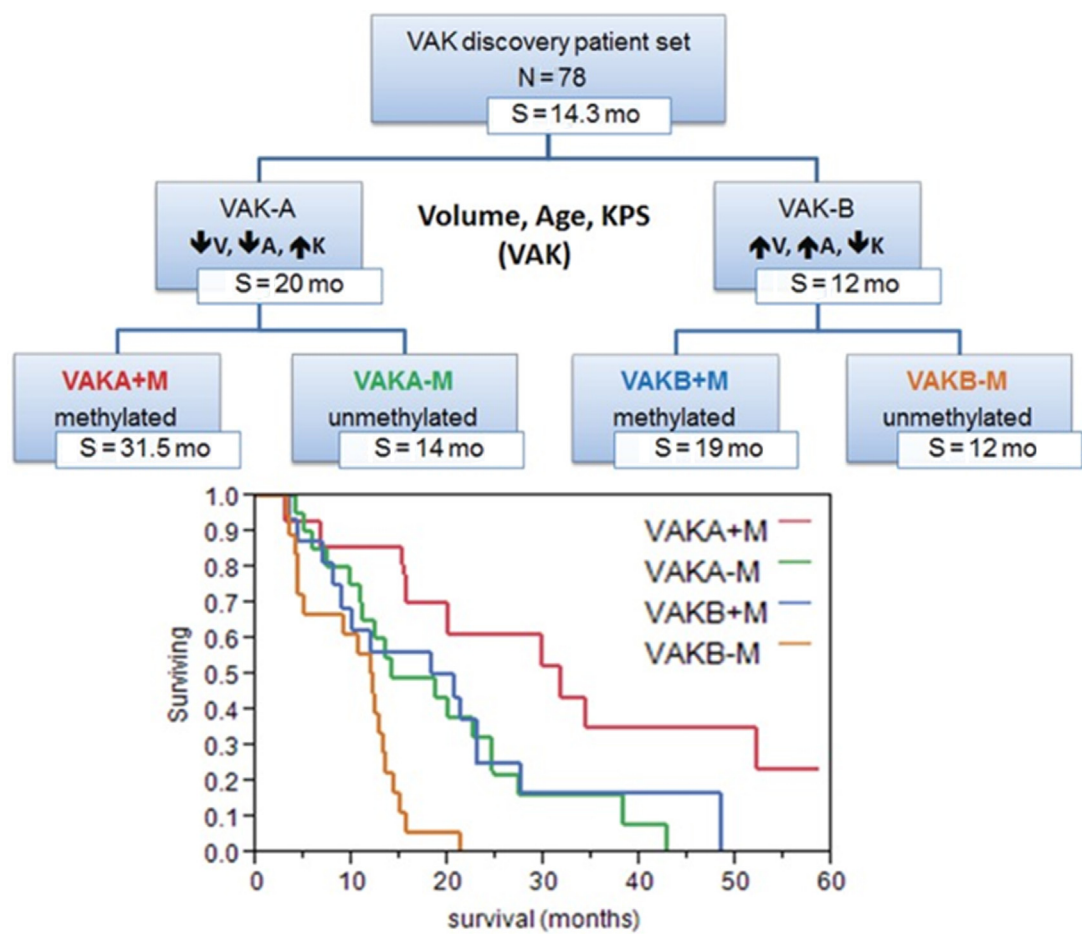
Fig. 2. VAK MGMT model for survival stratification. (*From* Zinn PO, Sathyan P, Mahajan B, Bruyere J, Hegi M, Majumder S, et al. A novel volume-age-KPS (VAK) glioblastoma classification identifies a prognostic cognate microRNA-gene signature. PLoS One. 2012;7(8):e41522.)

characteristics of this region. Zinn and colleagues[46] demonstrated that there was up-regulation of PERIOSTIN (POSTN) gene set and down-regulated microRNA-219 in the T2-FLAIR hyperintensity. PERIOSTIN was found to be promoting mesenchymal transition and invasion in GB and POSTN expression was up-regulated significantly in the mesenchymal subtype of GB.[46] Pope and colleagues[44] found that the incompletely enhancing tumor regions (regions defined as nonenhancing FLAIR hyperintense areas with suspicion of tumor infiltration) had distinct genetic profile compared with the enhancing tumor regions and demonstrated higher expression levels of the stem cell and oligo-dendrocyte lineage marker OLIG-246 as well as genes associated with secondary GB.

Necrosis

Necrosis is a hallmark of GB and is closely associated with shortened patient survival in high-grade gliomas.[47,48] Colen and colleagues[49] studied the phenomenon of cell death in GBs with respect to sex-specific differences and found overall lower volumes of necrosis on imaging in women compared with men. Women with higher volumes of necrosis had poor outcomes compared with men (6.5 months vs 14.5 months, respectively; $P = .01$). Larger area of necrosis in women was associated with MYC, an oncogenic transcription factor (via an oncogenic pathway), whereas in men it was associated with Tp53 (via an apoptotic pathway).[49] Van Meter and colleagues[50] explored intratumor genetic variations between the enhancing peripheral mass and a poorly enhancing central tumor core on contrast-enhanced T1-weighted MR imaging and found increased expression of genes

associated with cell migration, angiogenesis, cell survival, and integrin signaling in the enhancing core, with the poorly enhancing and low perfused core having an elevated rate of expression for hypoxia-induced gene. Yamashita and colleagues[51] found correlation between IDH1 status and area of necrosis. Barajas and colleagues[45] confirmed these findings by reporting the increased expression of genes associated with mitosis, angiogenesis, and apoptosis.

Restricted Diffusion on Diffusion-Weighted Imaging–Apparent Diffusion Coefficient

In tumor imaging, lower apparent diffusion coefficient (ADC) values are known to reflect areas of hypercellularity. Zinn and colleagues[52] studied ADC values in the nonenhancing, FLAIR hyperintense lesions of the tumor in 35 GB patients and found that lower ADC values (restricted diffusion) were seen in the peritumoral edematous/tumor-infiltrated tissue. These lower ADC values were correlated further with distinct genomic networks and differentially expressed genes that play a role in invasion.[52] ADC measurements have shown promise in predicting MGMT methylation status and patient survival.[53–55] Heiland and colleagues[56] studied the role of DTI-derived parameters in identification of gene expression pathways in 21 patients, which were correlated with biopsy tissue. They documented that GB with high fractional anisotropy had a worse prognosis and was associated with activation of the epithelial mesenchymal pathway, whereas higher mean diffusivity was suggestive of more favorable prognosis.[56] Hong and colleagues[41] were able to demonstrate ADC differences based on IDH1 and ATRX profiles of GBs.

Perfusion Status of the Tumor

Dynamic contrast–enhanced and dynamic susceptibility contrast MR perfusion are employed routinely in the presurgical evaluation and post-treatment follow-up of the brain tumors. Among all the perfusion parameters, cerebral blood volume (CBV) has been the most extensively studied. Barajas and colleagues[45] studied enhanced and nonenhanced portions of the tumor and correlated them with CBV and peak height values, and decreased percentage of signal recovery and ADC values. They documented that the genes associated with mitosis, angiogenesis, and apoptosis were significantly upregulated in contrast-enhanced regions compared with nonenhanced portion of the tumor (**Fig. 3**).[45,57] In a feasibility study using perfusion CT, Jain and colleagues[58] demonstrated positive correlation between higher perfusion parameters and proangiogenic genes and a negative correlation between these parameters and antiangiogenic genes. Jain and colleagues[59] using dynamic susceptibility contrast–enhanced T2-weighted MR perfusion from TCIA TCGA-GB collection, correlated tumor blood volume with patient survival, and determined its association with molecular subclasses of GB. They measured the mean relative CBV (rCBV) of the contrast-enhanced and nonenhanced regions and correlated with the genomic subclassification. They found that rCBV values had no statistical significance with regard to their molecular classification, but the rCBV max measurements were found to be a strong predictor of overall survival regardless of the molecular subtype.[59] Yamashita and colleagues[51] demonstrated the correlation between IDH1 status and tumor blood flow. Kong and colleagues[60] documented that CBV and cerebral blood flow–related radiomic features were significantly related to up-regulation of PDGF, EGFR, and VEGF pathways and down-regulation of the PTEN pathway.

MR Spectroscopy

Besides MR perfusion, MR spectroscopy has been used commonly in the evaluation of the brain tumor. Mutations of the IDH1 and IDH2 genes result in an over-reduction of the α-ketoglutarate 2-HG metabolite, leading to an accumulation of 2-HG. Choi and colleagues showed the existence of 2-HG and glutamate multiplets in patients with IDH-mutated grade II–III tumors with 100% sensitivity and specificity. A maximum 2-HG peak was identified at approximately 2.25 parts per million (ppm), near the γ-aminobutyric acid peak (2.2–2.4 ppm) and located to the left of the N-acetylaspartate peak, at 2.0 ppm.[61] Similar findings were also seen by Lazovic and colleagues[62] and Pope and colleagues[63] in their studies. In conclusion, documentation of the 2-HG peak is seen with IDH mutation gliomas, and its absence is consistent with IDH wild-type tumors. MR spectroscopy also has been found useful in documenting the treatment response with IDH1/2-mutant inhibitors. Heiland and colleagues[64] explored the relationship between the concentration of metabolites on MR spectroscopy and gene expression pathways. They were able to show spectral differences for different subtypes of GB. The high creatine metabolite was found to be correlated with proneural GB subtype, low creatine was related to mesenchymal subtype; low glutamate and glutamine metabolite was associated with neural subtype, and its high value was related to the classical subtype.[64]
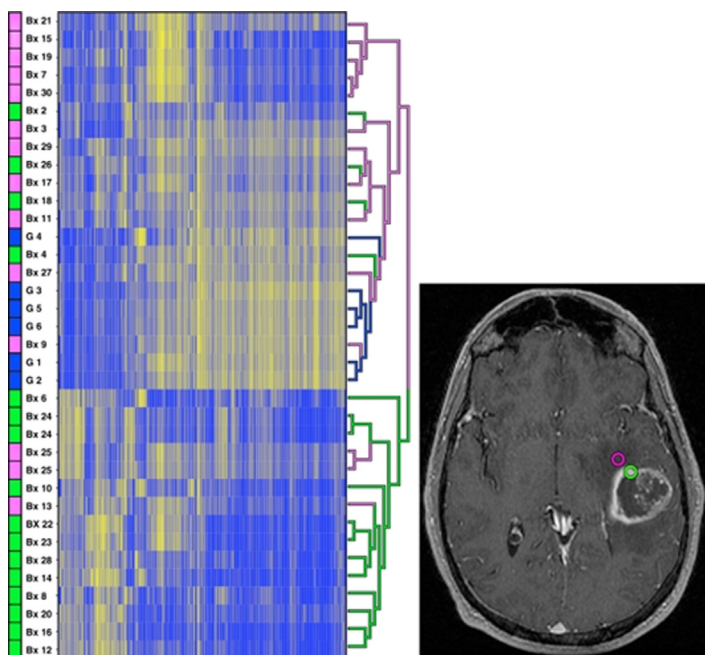
Fig. 3. Presence of contrast enhancement is predictive of GBM genetic expression pattern. (*Right*) Purple and green circles indicate nonenhancing and enhancing biopsy regions, respectively. (*Left*) Genetic expression map of all biopsy samples with hierarchical clustering of the 500 most variant genes shows clustering only by biopsy sample. Purple, nonenhancing samples; blue, gliosis samples; and green, enhancing samples. (*From* Ramon F. Barajas J, Hodgson JG, Chang JS, Vandenberg SR, Yeh R-F, Parsa AT, et al. Glioblastoma Multiforme Regional Genetic and Cellular Expression Patterns: Influence on Anatomic and Physiologic MR Imaging. Radiology. 2010;254(2):564-76.)

MOLECULAR CLASSIFICATION

Verhaak and colleagues[25] described a robust gene expression–based molecular classification of GBs into proneural, neural, classical, and mesenchymal subtypes that integrate multidimensional genomic data to establish patterns of somatic mutations and DNA copy number. Primary GBs represent the classical, mesenchymal, and neural subtypes. The mesenchymal and classical subtypes typically are associated with more aggressive, higher-grade gliomas. The classical subtype demonstrates a greater preponderance of EGFR amplification, decreased rates of *TP53* mutation, and *p16INK4A* and *p14ARF* deletion. One of the earliest studies based on TCGA data set used standardized features sets for image analysis, and associations between imaging features and Verhaak subtypes were assessed. The study found that the proneural subtype was more likely to include a tumor with low levels of contrast enhancement; and the mesenchymal subtype was noted to have lower proportion of nonenhanced T2/FLAIR hyperintense tissue compared with other subtypes.[65] Another study using semantic features found that volume analysis of different tumor regions was able to identify mesenchymal subtype with an area under the curve of 0.93 and *P*<.001. Again, mesenchymal subtypes were associated with lower ratios of nonenhanced T2/FLAIR hyperintensity to contrast enhancement and necrosis.[66] Jain and colleagues[59] correlated rCBV of the contrast-enhanced and nonenhanced portions of tumors in 50 patients from TCGA set with molecular subclasses and found no significant differences. The study found that rCBV measurements were predictive of overall patient survival independent of molecular classification, although including Verhaak subtypes improved the strength of such association.[59] Overview of studies using radiomic analysis for molecular classification is presented in the next section.

RADIOGENOMIC STUDIES USING RADIOMIC FEATURES

These studies use computer-derived quantitative data derived from clinical imaging, which are not visible to the human eye and not typically measurable in a reading room setting. These features give a detailed overview of the local and global heterogeneity of the tumor environment as seen on clinical images and can be extracted using conventional (human engineered) or deep learning approaches. These data are then analyzed using machine learning or deep learning methods for feature selection and radiogenomic correlation. The entire imaging data set typically is divided into a discovery cohort and a validation cohort. The radiomic features can be derived from clinical sequences, such as T2, FLAIR, T1, and T1 with contrast as well as from advanced imaging

techniques, such as diffusion, perfusion, and DTI. Detailed description of radiomic methodology is beyond the scope of this article and is extensively reviewed elsewhere.[67–69]

One of the earliest radiogenomic studies by Itakura and colleagues[70] extracted quantitative features related to shape, texture, and edge sharpness of each lesion and classified the entire cohort into 3 phenotypic clusters, namely premultifocal, spherical, and rim-enhancing. Each cluster was mapped to a unique set of molecular signaling pathways indicating differential molecular activities as well as differential survival probabilities.[70] Kickingereder and colleagues[71] correlated histogram features of anatomic, diffusion, and perfusion imaging with a broad selection of molecular features using machine learning algorithms. Based on MR imaging features, the investigators were able to predict EGFR amplification status and classic subtype with moderate accuracy, although the association strength was not sufficient for generation of a robust model.[71] In a study based on TCGA data set, convolutional neural network was trained to classify IDH1 mutation status, 1p/19q codeletion, and MGMT promoter methylation status based on imaging features. The study demonstrated an accuracy of 94% for IDH1, 92% for 1p/19q, and 83% for MGMT promoter methylations status classification.[72] Several studies have focused on individual molecular characteristics using the radiomic features for imaging phenotypes. For example, using only T2 imaging for texture analysis, Korfiatis and colleagues[73] were able to predict MGMT methylation status with 85% accuracy, whereas Li and colleagues[74] were able to predict the same with 80% accuracy using a multiparametric model using features derived from T1, T1 with contrast, T2, and T2/FLAIR images. In a radiogenomic study based on anatomic and perfusion imaging, the investigators were able to predict EGFRvIII mutation in GBs with 85.3% and 87% accuracy in discovery and validation cohort, respectively.[75] Another study based on perfusion imaging devised a within patient peritumoral heterogeneity index, which compared perfusion parameters of immediate and distant peritumoral edema. Using this index, EGFRvIII mutation was identified with accuracy of 89.9% and specificity of 92%, wherein tumors with this mutation demonstrated a highly infiltrative-migratory phenotype compared with a peritumoral confined vascularization seen in EGFRvIII tumors.[76]

In an attempt to interrogate the hypoxia pathway, Beig and colleagues[77] quantified radiomic texture descriptors of tumor heterogeneity, which were surrogates for tumor hypoxia, and evaluated their role in predicting patient survival. Hu and colleagues[78] used texture analysis techniques to assess genetic heterogeneity in enhancing and nonenhancing regions of GBs and generate predictive models for 6 driver genes. Highest accuracies were observed for PDGFRA (77.1%), EGFR (75%), CDKN2A (87.5%), and RB1 (87.5%), whereas the lowest accuracy was observed in TP53 (37.5%). Higher accuracies were identified using features derived from nonenhanced regions compared with enhancing segments.[78] Dextraze and colleagues[79] identified multiple spatial habitats based on texture features of various tumor regions in a set of 85 GBs from TCGA data set and demonstrated the association of each habitat with unique pathway alterations and association of some of the habitats with overall survival. The phenomenon of angiogenesis and the hypoxia pathway were studied using perfusion imaging in a study by Liu and colleagues.[80] Based on perfusion parameters, a distinct subset of GBs was identified with unique perfusion and molecular characteristics, which pointed to enrichment of angiogenesis and hypoxia pathway markers. This cohort also had poor survival at baseline and had significantly longer survival when treated with antiangiogenic therapy compared with the other subset.[80]

Finally, radiomics-based analysis also has been used for predicting molecular subclasses of GBs. In a study by Macyszyn and colleagues,[81] machine learning techniques were used to analyze radiomic features from multiparametric MR imaging. Using a training data set of 105 and a validation data set of 29 patients, the study demonstrated an accuracy of 76% in classification of GB subtypes.[81] In a subsequent study by Rathore and colleagues,[82] based on radiomic features, 3 distinct subtypes of GB were identified, each with distinct clinical outcome and molecular profile, and relationship between imaging subtypes and molecular subtypes was established (**Fig. 4**).

LIMITATIONS AND FUTURE DIRECTIONS
Reproducibility

Radiogenomics studies, in particular those using radiomic features, are a powerful way to analyze entire tumor environment to identify underlying genomic alterations. Studies so far have demonstrated extremely promising results; however, concerns for generalizability arising from limited radiomic feature robustness remain. These limiting factors can arise at different steps of image acquisition, segmentation, feature extraction, feature selection, and modeling.[83] The imaging community has identified this concern and arrived at a consensus that value of quantitative imaging biomarkers can be improved by reducing variability
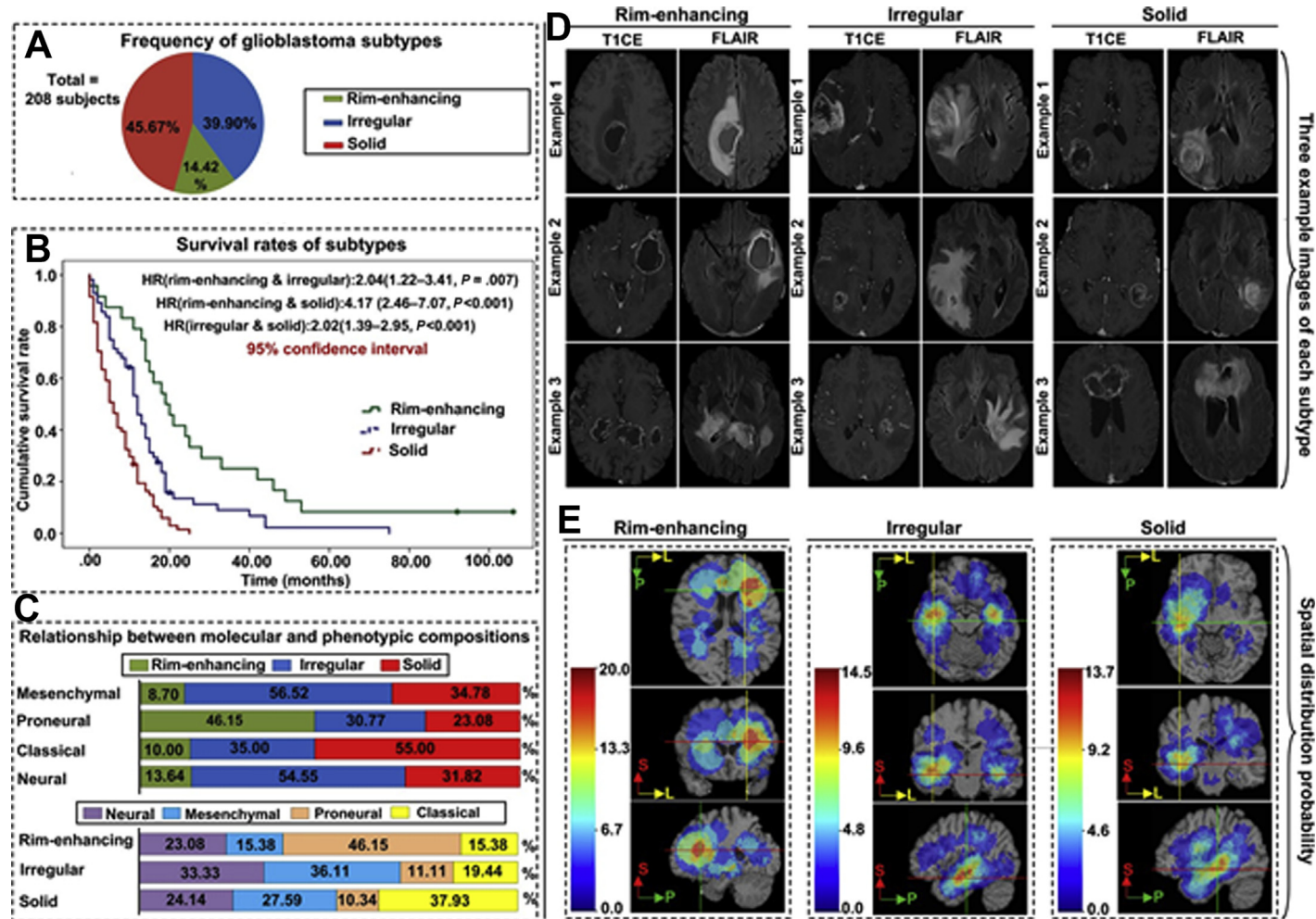
Fig. 4. GB imaging subtypes identified by the clustering process. (*A*) The frequency of each subtype. (*B*) Kaplan-Meier survival curves of the subtypes. (*C*) Relationship between the molecular composition (neural/mesenchymal/proneural/classical) and imaging subtypes (rim-enhancing/irregular/solid). (*D*) Three representative subjects of each subtype (closest to the mean of the cluster). (*E*) Spatial distribution probability of the tumors of each subtype. The color look-up tables show the probability of tumor existence. HR, hazard ratio. (*From* Rathore S, Akbari H, Rozycki M, Abdullah KG, Nasrallah MP, Binder ZA, et al. Radiomic MRI signature reveals three distinct subtypes of glioblastoma with different clinical and molecular characteristics, offering prognostic value beyond IDH1. Sci Rep. 2018;8(1):5087.)

arising from various steps in analysis (https://www.rsna.org/research/quantitative-imaging-biomarkers-alliance). The Quantitative imaging network (QIN) and Quantitative Imaging Biomarkers Alliance are major collaborative initiatives sponsored by imaging research communities to achieve set goals for biomarker standardization.[84,85] Similarly, efforts are under way to standardize region of interest labeling and segmentation to minimize bias and allow repeatable and reproducible analysis.[86] The Image Biomarker Standardization Initiative has led the effort in validating consensus-based reference values for a set of radiomic features to standardize the feature extraction process.[87] Emerging quantitative techniques, such as MR fingerprinting, with its high reproducibility and repeatability, may have a role to play in ensuring feature robustness in future radiomics studies.[88,89]

Data Size Considerations

Radiomics and radiogenomics studies are highly data intensive. Because the number of features extracted often is large, and sometimes larger than the sample size, overfitting the data always is a risk.[83] Deployment of appropriate feature selection methods can mitigate the problem to a certain degree. Using models that include patient demographics and clinical parameters should be considered so that the results are closer to the ground truth. Given the methodology, having a large, well-curated data set is necessary to achieve robust and reliable results. The QIN with its TCGA initiative has allowed investigators to build a collection of rich imaging, genomic, and clinical data sets. The Radiomics Signatures for Precision Diagnostics consortium on GB is a worldwide collaboration that aims to address the challenges associated with artificial intelligence and machine learning analyses in GBs.[90] Because these are retrospectively collected data sets, however, there is no way to standardize image quality. There is a need for a prospectively generated data repository with rich imaging, clinical, and omics features that will assure image standardization and allow robust analytics.

Translation from Bench to Bedside

A recent systematic review of radiomics applications in neuro-oncology has concluded that the current evidence is not sufficient to support use of radiomics studies in clinical setting.[91] Although the radiomics studies performed well in areas of feature selection and validation, the performance in the areas of protocol quality, reproducibility, biological/clinical validation, and clinical utility was deemed modest, at best. For radiomics and radiogenomics to be adopted successfully in the clinical practice, the steps outlined by National Institutes of Health in the biomarker development process need to be followed.[92] The key areas of technical validation, biological/clinical validation, and cost effectiveness need to be studied rigorously in a prospective approach. In parallel, efforts need to be directed toward conducting hypothesis-driven studies to test the performance of these techniques in a multi-institutional research setting. Until these gaps are bridged, translation of radiomics and radiogenomics from imaging laboratory to reading room remains out of reach.

SUMMARY

Radiogenomics studies offer a powerful way to characterize genomic and molecular characteristics of gliomas noninvasively, using semantic or radiomic features. Although current literature evidence is promising, significant work is needed before application of these techniques in day-to-day clinical practice.

CLINICS CARE POINTS

- Radiogenomics is the study of relationship between imaging features (radiophenotypes) and genetic/molecular profile of disease state, typically neoplasms.

- Current brain tumors research is focused on tumor genomics to identify novel therapeutic targets, devise personalized treatment options, and thereby improve individual patient outcomes.

- The radiomic features derived from clinical sequences, such as T2, FLAIR, T1, and T1 with contrast as well as from advanced imaging techniques, such as diffusion, perfusion, and DTI, can give a detailed overview of the local and global genomic heterogeneity of the tumor environment.

- The key areas of technical validation, biological/clinical validation, and cost effectiveness need to be studied rigorously in a prospective approach. Until these gaps are bridged, translation of radiomics and radiogenomics from imaging laboratory to reading room remains out of reach.

DISCLOSURE

None.

REFERENCES

1. Lander ES, Linton LM, Birren B, et al. Initial sequencing and analysis of the human genome. Nature 2001;409(6822):860–921.

2. Louis DN, Perry A, Reifenberger G, et al. The 2016 world health organization classification of tumors of the central nervous system: a summary. Acta Neuropathol 2016;131(6):803–20.

3. Lim-Fat MJ, Nayak L, Meredith DM. Genomic biomarker assessment in gliomas: impacts of molecular testing on clinical practice and trial design. Surg Pathol Clin 2020;13(2):209–15.

4. Lohmann P, Galldiks N, Kocher M, et al. Radiomics in neuro-oncology: Basics, workflow, and applications. Methods 2020. https://doi.org/10.1016/j.ymeth.2020.06.003.

5. Prior F, Smith K, Sharma A, et al. The public cancer radiology imaging collections of the cancer imaging archive. Sci Data 2017;4(1):170124.

6. Delgado-Lopez P, Corrales-Garcia E, Martino J, et al. Diffuse low-grade glioma: a review on the new molecular classification, natural history and current management strategies. Clin Transl Oncol 2017;19(8):931–44.

7. Delgado-López PD, Corrales-García EM. Survival in glioblastoma: a review on the impact of treatment modalities. Clin Transl Oncol 2016;18(11):1062–71.

8. Rich JN. Cancer stem cells: understanding tumor hierarchy and heterogeneity. Medicine (Baltimore) 2016;95(1 Suppl 1):S2–7.

9. Ohgaki H, Kleihues P. Genetic pathways to primary and secondary glioblastoma. Am J Pathol 2007;170(5):1445–53.

10. Mazurowski MA. Radiogenomics: what it is and why it is important. J Am Coll Radiol 2015;12(8):862–6.

11. Yan H, Parsons DW, Jin G, et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360(8):765–73.

12. Hartmann C, Hentschel B, Wick W, et al. Patients with IDH1 wild type anaplastic astrocytomas exhibit worse prognosis than IDH1-mutated glioblastomas, and IDH1 mutation status accounts for the unfavorable prognostic effect of higher age: implications for classification of gliomas. Acta Neuropathol 2010;120(6):707–18.

13. Reifenberger J, Reifenberger G, Liu L, et al. Molecular genetic analysis of oligodendroglial tumors shows preferential allelic deletions on 19q and 1p. Am J Pathol 1994;145(5):1175–90.

14. Comprehensive. Integrative genomic analysis of diffuse lower-grade gliomas. N Engl J Med 2015;372(26):2481–98.

15. Cairncross G, Wang M, Shaw E, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol 2013;31(3):337–43.

16. Jenkins RB, Blair H, Ballman KV, et al. A t(1;19)(q10; p10) mediates the combined deletions of 1p and 19q and predicts a better prognosis of patients with oligodendroglioma. Cancer Res 2006;66(20):9852–61.

17. Griffin CA, Burger P, Morsberger L, et al. Identification of der(1;19)(q10;p10) in five oligodendrogliomas suggests mechanism of concurrent 1p and 19q Loss. J Neuropathol Exp Neurol 2006;65(10):988–94.

18. Eckel-Passow JE, Lachance DH, Molinaro AM, et al. Glioma Groups Based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med 2015;372(26):2499–508.

19. Hegi ME, Diserens A-C, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997–1003.

20. Herrlinger U, Tzaridis T, Mack F, et al. Lomustine-temozolomide combination therapy versus standard temozolomide therapy in patients with newly diagnosed glioblastoma with methylated MGMT promoter (CeTeG/NOA–09): a randomised, open-label, phase 3 trial. Lancet 2019;393(10172):678–88.

21. Gilbert MR, Wang M, Aldape KD, et al. Dose-dense temozolomide for newly diagnosed glioblastoma: a randomized phase III clinical trial. J Clin Oncol 2013;31(32):4085.

22. Leu S, von Felten S, Frank S, et al. IDH/MGMT-driven molecular classification of low-grade glioma is a strong predictor for long-term survival. Neuro Oncol. 2013;15(4):469–79.

23. Kálovits F, Tompa M, Nagy Á, et al. Isocitrate dehydrogenase mutations in defining the biology of and supporting clinical decision making in glioblastoma. Ideggyogy Sz 2018;71(7–08):237–47.

24. Eskilsson E, Røsland GV, Solecki G, et al. EGFR heterogeneity and implications for therapeutic intervention in glioblastoma. Neuro Oncol 2018;20(6):743–52.

25. Verhaak RG, Hoadley KA, Purdom E, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell 2010;17(1):98–110.

26. Dunn GP, Rinne ML, Wykosky J, et al. Emerging insights into the molecular and cellular basis of glioblastoma. Genes Dev 2012;26(8):756–84.

27. Brennan CW, Verhaak RG, McKenna A, et al. The somatic genomic landscape of glioblastoma. Cell 2013;155(2):462–77.

28. An Z, Aksoy O, Zheng T, et al. Epidermal growth factor receptor and EGFRvIII in glioblastoma: signaling pathways and targeted therapies. Oncogene 2018;37(12):1561–75.

29. Zagzag D, Lukyanov Y, Lan L, et al. Hypoxia-inducible factor 1 and VEGF upregulate CXCR4 in glioblastoma: implications for angiogenesis and glioma cell invasion. Lab Invest 2006;86(12):1221–32.

30. Keunen O, Johansson M, Oudin A, et al. Anti-VEGF treatment reduces blood supply and increases tumor cell invasion in glioblastoma. Proc Natl Acad Sci U S A 2011;108(9):3749–54.

31. Young JS, Gogos AJ, Morshed RA, et al. Molecular characteristics of diffuse lower grade gliomas: what neurosurgeons need to know. Acta Neurochir (Wien) 2020;162(8):1929–39.

32. Delgado-López PD, Saiz-López P, Gargini R, et al. A comprehensive overview on the molecular biology of human glioma: what the clinician needs to know. Clin Transl Oncol 2020. https://doi.org/10.1007/s12094-020-02340-8.

33. Park S-H, Won J, Kim S-I, et al. Molecular testing of brain tumor. J Pathol Transl Med 2017;51(3):205–23.

34. Brennan C. Genomic profiles of glioma. Curr Neurol Neurosci Rep 2011;11(3):291–7.

35. Madhavan S, Zenklusen J-C, Kotliarov Y, et al. Rembrandt: helping personalized medicine become a reality through integrative translational research. Mol Cancer Res 2009;7(2):157–67.

36. Carrillo JA, Lai A, Nghiemphu PL, et al. Relationship between tumor enhancement, edema, IDH1 mutational status, MGMT promoter methylation, and survival in glioblastoma. AJNR Am J Neuroradiol 2012;33(7):1349–55.

37. Metellus P, Coulibaly B, Colin C, et al. Absence of IDH mutation identifies a novel radiologic and molecular subtype of WHO grade II gliomas with dismal prognosis. Acta Neuropathol 2010;120(6):719–29.

38. Paldor I, Pearce FC, Drummond KJ, et al. Frontal glioblastoma multiforme may be biologically distinct from non-frontal and multilobar tumors. J Clin Neurosci 2016;34:128–32.

39. Sonoda Y, Shibahara I, Kawaguchi T, et al. Association between molecular alterations and tumor location and MRI characteristics in anaplastic gliomas. Brain Tumor Pathol 2015;32(2):99–104.

40. Qi S, Yu L, Li H, et al. Isocitrate dehydrogenase mutation is associated with tumor location and magnetic resonance imaging characteristics in astrocytic neoplasms. Oncol Lett 2014;7(6):1895–902.

41. Hong EK, Choi SH, Shin DJ, et al. Radiogenomics correlation between MR imaging features and major genetic profiles in glioblastoma. Eur Radiol 2018;28(10):4350–61.

42. Ellingson BM, Lai A, Harris RJ, et al. Probabilistic radiographic atlas of glioblastoma phenotypes. AJNR Am J Neuroradiol 2013;34(3):533–40.

43. Zinn PO, Sathyan P, Mahajan B, et al. A novel volume-age-KPS (VAK) glioblastoma classification identifies a prognostic cognate microRNA-gene signature. PLoS One 2012;7(8):e41522.

44. Pope WB, Chen JH, Dong J, et al. Relationship between gene expression and enhancement in glioblastoma multiforme: exploratory DNA microarray analysis. Radiology 2008;249(1):268–77.

45. Barajas RF Jr, Phillips JJ, Parvataneni R, et al. Regional variation in histopathologic features of tumor specimens from treatment-naive glioblastoma correlates with anatomic and physiologic MR Imaging. Neuro Oncol 2012;14(7):942–54.

46. Zinn PO, Mahajan B, Sathyan P, et al. Radiogenomic mapping of edema/cellular invasion MRI-phenotypes in glioblastoma multiforme. PLoS One 2011;6(10):e25451.

47. Barker FG, Davis RL, Chang SM, et al. Necrosis as a prognostic factor in glioblastoma multiforme. Cancer 1996;77(6):1161–6.

48. Pope WB, Sayre J, Perlina A, et al. MR imaging correlates of survival in patients with high-grade gliomas. AJNR Am J Neuroradiol 2005;26(10):2466–74.

49. Colen RR, Wang J, Singh SK, et al. Glioblastoma: imaging genomic mapping reveals sex-specific oncogenic associations of cell death. Radiology 2015;275(1):215–27.

50. Van Meter T, Dumur C, Hafez N, et al. Microarray analysis of MRI-defined tissue samples in glioblastoma reveals differences in regional expression of therapeutic targets. Diagn Mol Pathol 2006;15(4):195–205.

51. Yamashita K, Hiwatashi A, Togao O, et al. MR imaging–based analysis of glioblastoma multiforme: estimation of idh1 mutation status. AJNR Am J Neuroradiol 2016;37(1):58–65.

52. Zinn PO, Hatami M, Youssef E, et al. Diffusion weighted magnetic resonance imaging radiophenotypes and associated molecular pathways in glioblastoma. Neurosurgery 2016;63(CN_suppl_1):127–35.

53. Cui Y, Ren S, Tha KK, et al. Volume of high-risk intratumoral subregions at multi-parametric MR imaging predicts overall survival and complements molecular analysis of glioblastoma. Eur Radiol 2017;27(9):3583–92.

54. Han Y, Yan LF, Wang XB, et al. Structural and advanced imaging in predicting MGMT promoter methylation of primary glioblastoma: a region of interest based analysis. BMC Cancer 2018;18(1):215.

55. Rundle-Thiele D, Day B, Stringer B, et al. Using the apparent diffusion coefficient to identifying MGMT promoter methylation status early in glioblastoma: importance of analytical method. J Med Radiat Sci 2015;62(2):92–8.

56. Heiland DH, Simon-Gabriel CP, Demerath T, et al. Integrative diffusion-weighted imaging and radiogenomic network analysis of glioblastoma multiforme. Sci Rep 2017;7:43523.

57. Ramon F, Barajas J, Hodgson JG, et al. Glioblastoma multiforme regional genetic and cellular expression patterns: influence on anatomic and physiologic MR imaging. Radiology 2010;254(2):564–76.

58. Jain R, Poisson L, Narang J, et al. Correlation of perfusion parameters with genes related to

angiogenesis regulation in glioblastoma: a feasibility study. AJNR Am J Neuroradiol 2012;33(7):1343–8.

59. Jain R, Poisson L, Narang J, et al. Genomic mapping and survival prediction in glioblastoma: molecular subclassification strengthened by hemodynamic imaging biomarkers. Radiology 2013;267(1):212–20.

60. Kong D-S, Kim J, Ryu G, et al. Quantitative radiomic profiling of glioblastoma represents transcriptomic expression. Oncotarget 2018;9(5):6336.

61. Choi C, Ganji S, DeBerardinis R, et al. 2-hydroxy-glutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012;18(4):624–9.

62. Lazovic J, Soto H, Piccioni D, et al. Detection of 2-hydroxyglutaric acid in vivo by proton magnetic resonance spectroscopy in U87 glioma cells overexpressing isocitrate dehydrogenase–1 mutation. Neuro Oncol 2012;14(12):1465–72.

63. Pope WB, Prins RM, Thomas MA, et al. Non-invasive detection of 2-hydroxyglutarate and other metabolites in IDH1 mutant glioma patients using magnetic resonance spectroscopy. J Neurooncol 2012;107(1):197–205.

64. Heiland DH, Wörner J, Haaker JG, et al. The integrative metabolomic-transcriptomic landscape of glioblastome multiforme. Oncotarget 2017;8(30):49178.

65. Gutman DA, Cooper LA, Hwang SN, et al. MR imaging predictors of molecular profile and survival: multi-institutional study of the TCGA glioblastoma data set. Radiology 2013;267(2):560–9.

66. Naeini KM, Pope WB, Cloughesy TF, et al. Identifying the mesenchymal molecular subtype of glioblastoma using quantitative volumetric analysis of anatomic magnetic resonance images. Neuro Oncol. 2013;15(5):626–34.

67. Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. Nat Rev Clin Oncol 2017;14(12):749–62.

68. Gore S, Chougule T, Jagtap J, et al. A review of radiomics and deep predictive modeling in glioma characterization. Acad Radiol 2020. https://doi.org/10.1016/j.acra.2020.06.016.

69. Soni N, Priya S, Bathla G. Texture analysis in cerebral gliomas: a review of the literature. AJNR Am J Neuroradiol 2019;40(6):928–34.

70. Itakura H, Achrol AS, Mitchell LA, et al. Magnetic resonance image features identify glioblastoma phenotypic subtypes with distinct molecular pathway activities. Sci Transl Med 2015;7(303):303ra138.

71. Kickingereder P, Bonekamp D, Nowosielski M, et al. Radiogenomics of glioblastoma: machine learning–based classification of molecular characteristics by using multiparametric and multiregional MR imaging features. Radiology 2016;281(3):907–18.

72. Chang P, Grinband J, Weinberg BD, et al. Deep-learning convolutional neural networks accurately classify genetic mutations in gliomas. AJNR Am J Neuroradiol 2018. https://doi.org/10.3174/ajnr.A5667.

73. Korfiatis P, Kline TL, Coufalova L, et al. MRI texture features as biomarkers to predict MGMT methylation status in glioblastomas. Med Phys 2016;43(6Part1):2835–44.

74. Li Z-C, Bai H, Sun Q, et al. Multiregional radiomics features from multiparametric MRI for prediction of MGMT methylation status in glioblastoma multiforme: a multicentre study. Eur Radiol 2018;28(9):3640–50.

75. Akbari H, Bakas S, Pisapia JM, et al. In vivo evaluation of EGFRvIII mutation in primary glioblastoma patients via complex multiparametric MRI signature. Neuro Oncol 2018;20(8):1068–79.

76. Bakas S, Akbari H, Pisapia J, et al. In vivo detection of EGFRvIII in glioblastoma via perfusion magnetic resonance imaging signature consistent with deep peritumoral infiltration: the φ-index. Clin Cancer Res 2017;23(16):4724–34.

77. Beig N, Patel J, Prasanna P, et al. Radiogenomic analysis of hypoxia pathway is predictive of overall survival in Glioblastoma. Sci Rep 2018;8(1):7.

78. Hu LS, Ning S, Eschbacher JM, et al. Radiogenomics to characterize regional genetic heterogeneity in glioblastoma. Neuro Oncol. 2017;19(1):128–37.

79. Dextraze K, Saha A, Kim D, et al. Spatial habitats from multiparametric MR imaging are associated with signaling pathway activities and survival in glioblastoma. Oncotarget 2017;8(68):112992.

80. Liu TT, Achrol AS, Mitchell LA, et al. Magnetic resonance perfusion image features uncover an angiogenic subgroup of glioblastoma patients with poor survival and better response to antiangiogenic treatment. Neuro Oncol 2017;19(7):997–1007.

81. Macyszyn L, Akbari H, Pisapia JM, et al. Imaging patterns predict patient survival and molecular subtype in glioblastoma via machine learning techniques. Neuro Oncol 2015;18(3):417–25.

82. Rathore S, Akbari H, Rozycki M, et al. Radiomic MRI signature reveals three distinct subtypes of glioblastoma with different clinical and molecular characteristics, offering prognostic value beyond IDH1. Sci Rep 2018;8(1):5087.

83. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology 2016;278(2):563–77.

84. Sullivan DC, Obuchowski NA, Kessler LG, et al. Metrology standards for quantitative imaging biomarkers. Radiology 2015;277(3):813–25.

85. Farahani K, Tata D, Nordstrom RJ. QIN benchmarks for clinical translation of quantitative imaging tools. Tomography 2019;5(1):1–6.

86. Bakas S, Akbari H, Sotiras A, et al. Advancing the cancer genome atlas glioma MRI collections with

expert segmentation labels and radiomic features. Sci Data 2017;4:170117.

87. Zwanenburg A, Vallières M, Abdalah MA, et al. The image biomarker standardization initiative: standardized quantitative radiomics for high-throughput image-based phenotyping. Radiology 2020;295(2): 328–38.

88. Körzdörfer G, Kirsch R, Liu K, et al. Reproducibility and repeatability of MR fingerprinting relaxometry in the human brain. Radiology 2019;292(2):429–37.

89. Dastmalchian S, Kilinc O, Onyewadume L, et al. Radiomic analysis of magnetic resonance fingerprinting in adult brain tumors. Eur J Nucl Med Mol Imaging 2020. https://doi.org/10.1007/s00259-020-05037-w.

90. Davatzikos C, Barnholtz-Sloan JS, Bakas S, et al. AI-based prognostic imaging biomarkers for precision neuro-oncology: the ReSPOND consortium. Neuro Oncol 2020;22(6):886–8.

91. Park JE, Kim HS, Kim D, et al. A systematic review reporting quality of radiomics research in neuro-oncology: toward clinical utility and quality improvement using high-dimensional imaging features. BMC Cancer 2020;20(1):29.

92. O'Connor JP, Aboagye EO, Adams JE, et al. Imaging biomarker roadmap for cancer studies. Nat Rev Clin Oncol 2017;14(3):169–86.