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TOPIC REVIEW

Radiomics for precision medicine in glioblastoma

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Abstract

Introduction Being the most common primary brain tumor, glioblastoma presents as an extremely challenging malignancy to treat with dismal outcomes despite treatment. Varying molecular epidemiology of glioblastoma between patients and intratumoral heterogeneity explains the failure of current one-size-fits-all treatment modalities. Radiomics uses machine learning to identify salient features of the tumor on brain imaging and promises patient-specific management in glioblastoma patients.

Methods We performed a comprehensive review of the available literature on studies investigating the role of radiomics and radiogenomics models for the diagnosis, stratification, prognostication as well as treatment planning and monitoring of glioblastoma.

Results Classifiers based on a combination of various MRI sequences, genetic information and clinical data can predict non-invasive tumor diagnosis, overall survival and treatment response with reasonable accuracy. However, the use of radiomics for glioblastoma treatment remains in infancy as larger sample sizes, standardized image acquisition and data extraction techniques are needed to develop machine learning models that can be translated effectively into clinical practice.

Conclusion Radiomics has the potential to transform the scope of glioblastoma management through personalized medicine.

Keywords Glioblastoma · Neuro-oncology · Radiomics · Radiogenomics · Primary brain tumor

Glioblastoma

Glioblastoma has an incidence of 3.22 per 100,000 and median overall survival (OS) of 14.6 months following standard treatment, which includes a combination of surgical resection, radiation therapy and chemotherapy [1]. This "one-size-fits-all" model for the treatment of glioblastoma is now being questioned following research on various pathways implied in intratumoral heterogeneity, arising as a result of genetic and epigenetic makeup, levels of protein

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expression, metabolic or bioenergetic behavior, microenvironment biochemistry and structural composition [2]. Consequently, features differ on histopathology and imaging across patients as well as spatially throughout a single tumor [3–5]. Personalized treatment protocols targeting individual patients' tumor characteristics are thus being increasingly advocated for improved success rates in glioblastoma management [4, 6, 7].

Radiomics and radiogenomics

Radiomics is an emerging application of neuroimaging where advanced computational methods are used to quantitatively extract characteristics from clinical images that are too complex for a human eye to appreciate [8, 9]. These imaging characteristics, called "features" reflect tumor characteristics and inner organization as well as the tumor microenvironment [9]. Radiomics is a multi-step process including the acquisition and preprocessing of images, segmentation, feature extraction and selection, and advanced statistics using machine learning (ML) algorithms (Fig. 1). The pipeline of radiomics is highly collaborative and involves contributions from clinicians, molecular biologists, statisticians, and bioengineers [8].

Radiomics-derived imaging phenotypes are associated with molecular markers to create 'radiogenomics' models [5]. It is a rapid and reproducible tool to evaluate tumor subtype, mutation status and intratumoral heterogeneity; and non-invasively predicts tumor progression, survival and response to targeted therapies using these characteristics [5, 8]. Radiogenomics offers more information as opposed to surgical biopsy in view of spatial tumor heterogeneity [8], especially useful for genomic profiling in recurrent glioblastoma which is driven by different clonal populations with varying hypermutations and evasion mechanisms [10]. Thus, clinical decision support systems using radiomics will form the base for precision medicine [9].

Applications of radiomics in glioblastoma management

Radiomics analysis has been widely studied for its use in subtyping brain tumors, predicting prognosis and treatment planning, supporting its potential use as a biomarker. Combining radiomics analysis with clinical and genetic information can remarkably enhance the utility of these models.

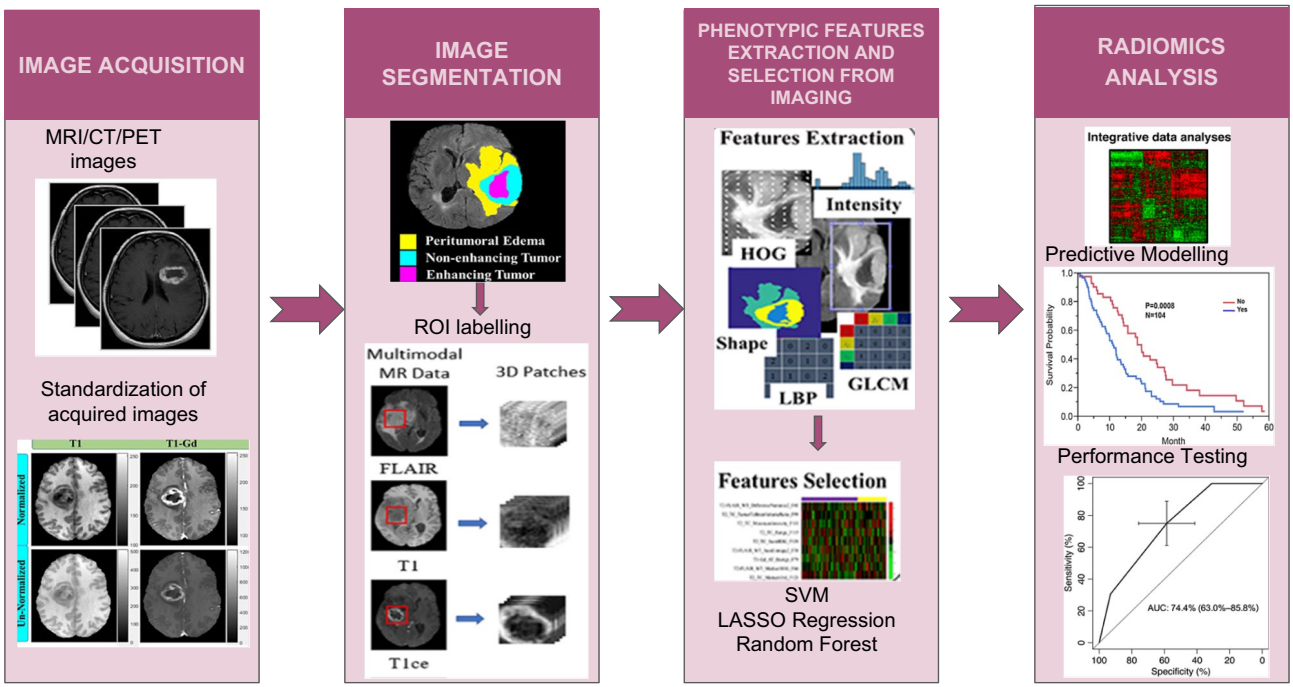

Fig. 1 Pipeline showing radiomics workflow. Acquired clinical images are subjected to standardization and segmentation to extract Regions Of Interest (ROI). After selecting relevant features, advanced statistical analysis is performed to classify and correlate radiomic features. (Images taken from these sources: Image acquisition—https://www.mdpi.com/2072-6694/11/8/1148. Segmentation—https://www.frontiersin.org/articles/10.3389/fncom.2020.00061/full. Feature extraction and selection- https://www.frontiersin.org/articles/10.3389/fncom.2019.00058/full. Analysis—https://www.frontiersin.org/articles/10.3389/fnins.2019.00966/full. Analysis—https://bmcmedgenomics.biomedcentral.com/articles/10.1186/1755-8794-7-30)

Diagnosis and classification of glioblastoma

Simple features on structural MRI such as tumor size, location and enhancement patterns have been used to predict histopathological subtypes of glioblastoma. Extracting complex features using image-processing software and combining with advanced MRI modalities can further improve the accuracy of these models (Table 1).

Tumor location

It is well known that the location of the tumor affects the outcomes in patients with glioblastoma. A "probabilistic radiographic atlas" of more than 500 glioblastoma patients showed associations between stereospecific frequency of tumor occurrence with age, extent of resection, genetic expression, and survival data. Interestingly, regions closer to subventricular zone were seen to have MGMT unmethylated, mesenchymal, and EGFR-amplified tumors [17], supporting their invasive nature and poor prognosis [38]. Another study showed correlation of tumor phenotypes with their spatial distribution [30]. A comparison between solitary and multicentric glioblastoma revealed upregulation of genes responsible for tumor cell motility and invasiveness and poor prognosis in the multicentric radiophenotype [22]. Thus, tumor location and multicentricity can give important clues to the cell of origin and tumor behavior.

Tumor size and contrast enhancement patterns

The correlation between tumor sizes and volume of different components (enhancing, necrosis and edema) is well established [27]. Previously, 'VASARI', a semi-quantitative feature set including tumor volumes, was employed to predict tumor subtypes and survival [15, 39]. In the VAK classification, a scoring system was developed to create phenotypes using tumor volumetry in combination with age and KPS annotation (Fig. 2) [35]. Volumetry was incorporated in a radiogenomics model where it was combined with DNA microarray analysis to train classifiers that can predict gene-expression patterns and survival. They showed that a high ratio of contrast-enhancing volume to the necrotic tumor volume (C:N) could predict overexpression of EGFR, an important therapeutic target [40]. In another radiogenomic study based on The Cancer Genome Atlas (TCGA) data, stratification into high and low FLAIR radiophenotypes reflected underlying edema and cellular invasion in glioblastoma, as they were associated with genes and microRNAs involved in cancer and cellular migration [36]. MRI volumetric features are predictive of several cancer-relevant, drug-targetable DNA mutations in glioblastoma. TP53, RB1, NF1, EGFR, and PDGFRA mutations could each be significantly predicted by at least one imaging feature [18]. These studies provide a basis for genomic profiling and non-invasively selecting patients for personalized therapies using tumor volumetry.

Radiomics can be used to distinguish solitary brain metastasis from glioblastoma on structural MRI. Artzi et al. developed an excellent classifier (AUC 0.96) with support vector machine (SVM) using post-contrast T1 weighted (T1CE) MRI. However, performance decreased when subtypes of brain metastasis were attempted to classify [11]. In another study, contrast-enhancing and peritumoral hyperintense masks in T2-weighted (T2W) MRI-based deep learning model showed best performance (area under curve AUC 0.956) compared to the traditional machine learning model (AUC 0.890) and human readers (AUC 0.774) [12]. However, when Shin et al. utilized both T1CE and T2W sequences to develop a 2D CNN, they only achieved reasonable accuracy implying no clear benefit of combining the two modalities [37].

Texture

Texture is a chief radiomic feature utilized for glioblastoma phenotyping. In one study, a gray-level co-occurrence matrix (GLCM) approach was employed for extracting phenotypic texture features for necrosis, active tumor, and edema on structural MRI. Features were significant predictors (p value < 0.01) of prognosis but in areas of active tumor only [41]. Another study was able to predict MGMT methylation status using space-frequency texture analysis based on the S-transform in T2W MRI, albeit with an accuracy of 71%, requiring better algorithms [16]. Other studies based on texture features were able to predict MGMT methylation status with reasonable accuracy [21, 20].

Occasionally, high-grade gliomas (WHO Grade III and glioblastoma) may have the same MRI appearance as low-grade gliomas. Classifiers using texture along with size, shape, intensity, and histogram features can be used to differentiate low-grade from high-grade gliomas. Performance of these classifiers varies with the algorithm used, the best performance was observed with SVM (AUC 0.932) and Random forest (AUC 0.921) [28, 14].

Advanced MRI sequences and multimodal analyses

Advanced sequences such as Diffusion and Perfusion MRI have been extensively used in brain tumors to evaluate invasiveness, angiogenesis, and tumor behavior. Raw tumor features from structural MRI and delta-radiomic features from dynamic susceptibility contrast (DSC) perfusion MRI were extracted to differentiate low-grade gliomas from high-grade gliomas. This classifier reached an AUC of 0.94 [19]. However, a Cochrane meta-analysis on 7 studies to differentiate untreated solid and non-enhancing low-grade from

Table 1 Application of radiomics in glioblastoma diagnosis and classification

Authors and reference no	Year	Study sample (*n*)	Task	Machine learning algorithm	Performance parameter
Artzi et al. [11]	2019	Glioblastoma and brain metastasis (439)	Differentiation between glioblastoma and brain metastasis	Support vector machine	Accuracy 0.85, sensitivity 0.86, specificity 0.85, AUC 0.96
Bae et al. [12]	2020	Glioblastoma and metastases (248)	Distinguishing glioblastoma from single brain metastasis	Deep learning	AUC 0.956, sensitivity 90.6%, specificity 88.0%, and accuracy 89.0%
Barajas Jr et al. [13]	2012	newly diagnosed glioblastoma (51)	Histopathologic correlation of MRI features	Mixed effect models	
Cho et al. [14]	2018	High grade and low grade gliomas, BraTS 2017 (285)	Glioma grading	Random forest	AUC 0.9213
Colen et al. [15]	2014	Treatmentnaïve glioblastoma, TCIA (104)	Radiogenomics in invasive phenotype	Robust multi-array (RMA)	
Drabycz et al. [16]	2010	Newly diagnosed GBM (59)	Predicting MGMT methylation status	Bicubic interpolating kernel	Accuracy 71%
Ellingson et al. [17]	2013	de novo glioblastoma (507)	Probabilistic radiographic atlases (tumor locations indicative of cells of origin)	Mutual information algorithm/ ADIFFI analysis	
Gutman et al. [18]	2015	Glioblastoma, TCIA (76)	Predicting somatic mutations		AUC 0.646—0.722
Jeong et al. [19]	2019	High-grade and lowgrade gliomas (25)	Glioma grading	Random forest	Accuracy 0.950 HG and 0.850 for LG; AUC 0.94
Hajianfar G et al. [20]	2019	Glioblastoma with known MGMT methylation status (82)	Predicting MGMT methylation status	Decision Tree classifier	AUC 0.78
Korfiatis P et al. [21]	2016	Glioblastoma with known MGMT methylation status (155)	Predicting MGMT methylation status	Support vector machine	AUC 0.85, sensitivity 0.803, specificity 0.81
Kong et al. [22]	2016	Treatmentnaïve GBM (51)	Phenotyping multicentric GBM	Shortest path algorithm	
Lee et al. [23]	2019	newly diagnosed GBM (123)	Predicting IDH1 mutation status	–	Prediction rate 70.3%-87.3%, accuracy 66.3%83.4% in the external validation set
Li et al. [24]	2018	Glioblastoma (133 training, 60 validation cohort) (193)	Predicting MGMT methylation status	Random forest	AUC = 0.88, accuracy = 80% Radiomics model
Lin et al. [25]	2017	8 PCNSL and 36 glioblastoma (44)	Differentiation of glioblastoma and primary CNS lymphoma	Histogram analysis	AUC 0.83 for mean ADC
Suh et al. [26]	2018	54 PCNSL and 23 atypical glioblastoma (77)	Differentiation of glioblastoma and primary CNS lymphoma	Random forest	Mean AUC 0.921 of the radiomics classifier
Naeini et al. [27]	2013	Glioblastoma (46)	Associating imaging features with mesenchymal subtype	Quantitative volumetric analysis	Volume of contrast enhancement: AUC 0.78 central necrosis: AUC = 0.73
Nakamoto et al. [28]	2019	Grade III and IV glioma (224)	Glioma grading	Random forest	Accuracy 0.806, sensitivity 0.822, specificity 0.773, AUC 0.800
Pope et al. [29]	2012	Newly diagnosed glioblastoma Upfront bevacizumab -treated (38)	Tumor stratification (gene expression in high-versus-low ADC tumors)	Positive Pixel Count and Nuclear Algorithms	
Rathore et al. [30]	2018	de novo glioblastoma (261)	Imaging based phenotypes for risk-stratification	Support vector machine	Accuracy 80.19% within subtypes, 73.58% across all patients

Table 1 (continued)

Authors and reference no	Year	Study sample (*n*)	Task	Machine learning algorithm	Performance parameter
Sasaki et al. [31]	2019	Newly diagnosed GBM patients (201)	Predicting MGMT status	LASSO	Accuracy 67%, Sensitivity 67%, Specificity 66%, Positive predictive value 67%, Negative predictive value 67%, Prevalence of pMGMT methylation 50%
Tian et al. [32]	2018	Grades II, III, and IV gliomas (153)	Glioma grading	Support vector machine	Accuracy 96.8%, AUC 0.987 LGGs vs HGGs; accuracy 98.1%, AUC 0.992 for grades III vs IV
Xi et al. [33]	2018	GBM patients (98)	Predicting MGMT methylation status	Support vector machine	Training: accuracy 86.59% validation: accuracy 80%
Xi et al. [33]	2018	Glioblastoma with known MGMT methylation status (98)	Predicting MGMT methylation status	Support vector machine	Training: accuracy 86.59%, validation: accuracy of 80%
Zhang et al. [34]	2017	High grade and low grade gliomas (120)	Glioma grading	Support vector machine	Accuracy 0.945
Zinn et al. [35]	2012	Glioblastoma, TCIA (142)	Patients stratification		
Zinn et al. [36]	2011	Glioblastoma, TCIA (78)	Radiogenomic mapping of edema/cellular invasion	Ingenuity pathway analysis (IPA)	
Shin et al. [37]	2021	Glioblastomaand solitary brain metasasis patients (598)	Differentiation of glioblastoma from solitary brain metastasis	Deep learning	Accuracy 89%, AUC 0.889

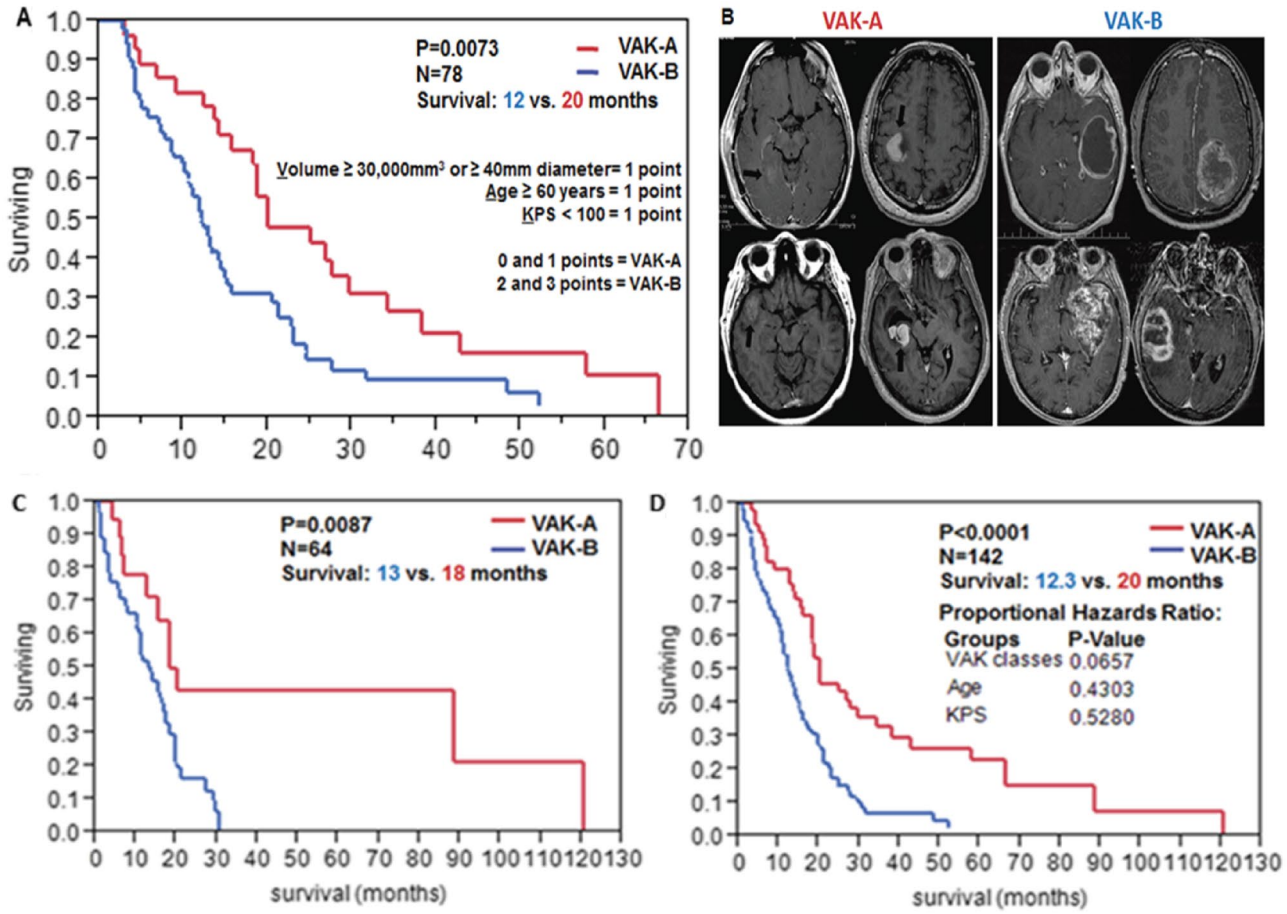

Fig. 2 Volume, Age, KPS (VAK) classification and phenotype. *V*olume, *A*ge, *K*PS (VAK)-A and B classes showing (**A**) Kaplan Meier survival plot (**B**) representative MRI images for VAK-A and VAK-B patients and (**C**) VAK-A and VAK-B survival validation in an independent patient set ($N=64$) and (**D**) combination of the discovery and validation set ($N=142$) for patient with full VAK annotation including the Proportional Hazards Model correcting for Age and KPS. (Source https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0041522)

high-grade gliomas using DSC MRI features (rCBV and Ktrans) reported wide range of estimates for both sensitivity and specificity, making these parameters less reliable [42]. Diffusion MRI was employed to compare the expression of various genes between the high- versus low- Apparent Diffusion Coefficient (ADC) tumors in a subset of patients. High-ADC tumors were found to have higher expression of 13 genes, 6 of which encode for extracellular matrix (ECM) molecules including collagen or collagen-binding proteins, suggesting a role of these genes in pro-invasive phenotype [29]. In another study, physiologic MRI was correlated with stereotactic image-guided biopsies to differentiate contrast-enhancing and nonenhancing tumor areas. DSC MRI was useful for identifying tissue specimens with higher tumor proliferation, necrosis, and vascular hyperplasia in the contrast-enhancing component of the lesion, while diffusion MRI may be useful to detect infiltrating tumors in the non-enhancing region. This is of particular interest for defining tumor burden in non-enhancing regions, where distinguishing reactive edema from biologically active infiltrative tumor is clinically important. In this study, accuracy of the results could be confounded by the misregistration arising as a result of brain shift [13].

MR imaging features of Primary CNS Lymphoma (PCNSL) and glioblastoma overlap, with differing survival outcomes and treatment options. In a study where perfusion and diffusion-weighted MRI were used to differentiate glioblastoma from lymphoma, mean ADC and plasma volume (rVp) were higher in the glioblastoma compared to PCNSL. Moreover, mean ADC was superior (AUC 0.83) to rVp and permeability transfer constant (Ktrans). This was true for contrast-enhancing regions only, possibly due to increases in tumor cellularity, microvascular permeability, and vascular proliferation [25]. In another study, ADC was outperformed by a multi-parametric (T1WCE, post-contrast T2W and FLAIR) and multiregional radiomics classifier with AUC

0.921 [26]. This questions the benefit of including advanced sequences in classifier in the presence of conventional MRI.

Other studies have explored the utility of multiparametric MRI to create more accurate radiomic models for tumor subtyping, grading and predicting mutational status. Rathore et al. used 267 multiparametric MRI based radiomic features, extracted from T1-weighted (T1W), T2W, T1CE, T2 FLAIR, DSC, and DTI to subtype de novo glioblastoma into three imaging phenotypes. For example, the solid subtype was characterized by highly uniform vascularization, highest cell densities, small-sized edema, moderately spherical and well-circumscribed appearance, with peritumoral edematous tissue having signs of heterogeneous neovascularization. This subtype had a predilection for the right temporal lobe and was associated with the worst prognosis. A personalized treatment regimen would involve very aggressive peritumoral resection and radiation dose escalation in these tumors [30]. Combining various MRI sequences can also improve classifier accuracy for tumor grading [32, 34]. Classifier performance also increased using MRI features from multiregional and multiparametric structural MRI to predict MGMT methylation status in glioblastoma [33, 24]. Similarly, IDH 1 mutation status was predicted using radiomic features on multiparametric MRI with enhanced accuracy when age and multiple regions were included [23].

Prognostication of glioblastoma

It is increasingly important for physicians to understand an individual patient's prognosis and adjust their therapy accordingly. For this reason, a large number of studies aimed to predict outcomes using radiomics alone and augmented with clinical data, genomics, and proteomics can be used. (Table 2).

Conventional MRI features

Studies have used various features extracted from conventional MRI to predict patient outcomes in glioblastoma. Longer median survival was associated with higher sphericity, surface-to-volume ratio and edge enhancement of glioblastoma lesions on T1W MRI [54]. Lao et. al divided features into 'handcrafted features' and 'deep features' to create a feature signature, which when coupled with clinical risk factors such as age and Karnofsky Performance Score, was able to predict overall survival (OS). Compared with the predictive ability of traditional risk factors, the proposed feature signature achieved a superior prediction of OS (C-index = 0.739) [49]. Similar combined models reached C-index of 0.974 [56].

Texture, tumor shape and volumetric features were extracted, and combined with age to produce a model that would predict short-term, mid-term, and long-term OS [56, 53]. Zhou et al. went one step further and identified spatial-based characteristics from tumor sub-regions that can be used to predict survival time in patients [57]. Similarly, Chaddad et al. found three texture features extracted from active part of the tumors that significantly predicted survival outcomes compared to the necrotic and edematous parts [41]. Moreover, these radiomic models could predict survival in different molecular subtypes as well [55]. Addition of location-based features of brain tumors to radiomic features extracted from conventional MRI enhanced the ability of a model to predict OS of patients by 9%. Furthermore, classifying groups according to resection status can also increase the accuracy of such prediction models [58]. Verma et al. used MRI features to create a radiomics risk score for predicting PFS. With a concordance index of 0.80, these features also correlated well with histopathologic attributes associated with glioblastoma aggressiveness. Such scores can be easily utilized in clinical settings [59].

Advanced MRI features

Advanced MRI modalities have also been also explored to predict glioblastoma patient outcomes [52]. It was seen that high rCBV in the non-enhancing region of tumor was predictive of worsening OS and Progression-free Survival (PFS) [48]. ADC histogram analysis was useful to predict PFS in newly diagnosed as well as recurrent glioblastoma [29, 60]. In these studies, low ADC predicted poor outcomes. Models incorporating both conventional and advanced MRI sequences may show better performance at predicting the prognosis.

Radiogenomics and proteomics

MGMT promoter hypermethylation is associated with better prognosis and response to therapy. This mutational status alongwith IDH has been combined with radiomic features from structural MRI to stratify patients based on overall survival producing more robust radiomics-based prognostic models [44, 51]. Zinn et al. stratified VAK annotated cases further with molecular signatures and found a 10.5 months' additional survival benefit for the group with *MGMT* promoter methylation [15]. In another study, glioblastomas were first divided into groups based on vascularization (rCBV values). It was seen that MGMT methylation was a positive predictive factor for OS ($p = 0.003$, AUC = 0.70) in the moderately vascularized tumors. However, there was no significant effect of MGMT methylation in the highly vascularized tumors ($p = 0.10$, AUC = 0.56) [45]. Contrastingly, some studies did not find any significant association of prognosis with MGMT promoter hypermethylation [54, 31]. This could be due to insufficient feature selection methods.

Table 2 Application of radiomics in glioblastoma survival prediction

Authors and reference nos	Year	Study sample (*n*)	Predictors of survival	Machine learning algorithm	Performance parameter
Beig et al. [43]	2018	Glioblastoma (115)	Radiomics features + expression profile of 21 hypoxiaassociated genes	Random forest and information gain	Combined Cindex = 0.69 training set, 0.83 on validation set
Choi et al. [44]	2020	Glioblastoma (120)	Radiomics + Clinical + MGMT and IDH-1 status	Deep learning/CNN	Combined overall and progression-free survival AUC 0.73 and 0.67
Chaddad et al. [41]	2016	Glioblastoma, TCIA (40)	Radiomics	Decision trees (DT)	Accuracy 79.31, sensitivity 91.67, and specificity 98.75%
Diehn et al. [40]	2008	Glioblastoma (25)	Radiomics (predictive of gene-expression pattern)	Two-step algorithm	–
Fuster-Garcia et al. [45]	2021	NCT034393 32 clinical study (96)	MGMT methylation and rCBV	Cox regression	AUC 0.70 for MGMT
Gutman et al. [39]	2013	Glioblastoma, TCIA (75)	Radiomics (predictive of molecular profile)	Cox regression	–
Hsu et al. [46]	2020	Glioblastoma (116)	Radiomics features predictive of Immunophenotypes	Random forest and information gain	Accuracy 79%
Kickingered er et al. [47]	2016	Newly diagnosed glioblastoma (181)	Radiomics + Clinical + Molecular	Cox regression	Prediction error reduced by 36% for PFS and 37% for OS
Jain et al. [48]	2014	GBM (45)	Clinical + genomic biomarkers + imaging of the nonenhancing component	Random forest and information gain	Joint imaging and clinical model AUC 0.69
Lao et al. [49]	2017	Glioblastoma (112)	Radiomics features + clinical factors	Pre-trained CNN via transfer learning/ deep learning	Combined model Cindex = 0.739
Liao et al. [50]	2019	Glioblastoma, TCIA (137)	Radiomics (predictive of gene-expression patterns)	Gradient boosting decision tree	Accuracy 0.81, AUC of the short and long survival time class 0.79 and 0.81
Molitoris et al. [51]	2017	Supratentori al GBM initiated TMZ-based concurrent chemothera py	Age, gender, MGMT status, performance status, resection extent, race, tumor site	Cox regression	–
Park et al. [52]	2020	Newly diagnosed glioblastoma (216)	Multiparametric MR prognostic model (radiomics score + clinical predictors)	Cox regression	C-index 0.74
Sanghani et al. [53]	2018	GBM patients from the BraTS 2017 dataset (163)	Radiomics	Support vector machine classificatio n	Accuracy 97.5%
Sasaki et al. [31]	2019	Newly diagnosed GBM (201)	Radiomics + MGMT status	Supervised principal component analysis (SPCA)	
Tixier et al. [54]	2019	GBM (159)	Radiomics + MGMT status	–	
Yang et al. [55]	2015	De novo GBM (82)	Radiomics	Random forest	AUC 0.69 for 12 month survival status
Zhang et al. [56]	2019	GBM (105)	Radiomics + clinical	Logistic regression	Training: C index, 0.971, validation: C-index 0.974
Zhou et al. [57]	2017	Glioblastoma (54)	Image-based spatial characteristics in tumor subregions	Support vector machine	Accuracy 87.50% (dataset 1) 86.36% (dataset 2)
Soltani M et al. [58]	2021	BraTS 2019 data	Predicting survival using location based features	Linear, regression, random vector forest, support regression	

Table 2 (continued)

Authors and reference nos	Year	Study sample (*n*)	Predictors of survival	Machine learning algorithm	Performance parameter
Verma R et al. [59]	2020	Glioblastom a patients (156)	Assessingfeatures that are prognostic for progression-free survival	LASSO, Cox regression	Concordanc e index 0.80

Integrative models promise a reduction in prediction errors [44, 43]. Chaddad et al. created multi-omic integrative model using radiomic, clinical, protein expression and genetic features to predict the outcome for IDH1 wild-type glioblastoma patients which reached AUC of 78.24% [61]. Liao et al. extracted First order and multi-dimensional features from segmented lesions on FLAIR MRI and gave a feature importance score for feature selection [50]. When combined with genetic expression, the Gradient Boosting Decision Tree model predicted both short-term and long-term survival with an accuracy of 0.81. While six metagenes showed significant interactive effects with image features, this study was limited by unavailability of complete genomic data [50].

Immunophenotypes in glioblastoma are important as they predict response to immunotherapy and outcomes. Hsu et al. used radiomic immunophenotyping models to predict patient prognosis [62]. They showed that the phenotype with the worst prognosis comprised highly enriched myeloid-derived suppressor cells and lowly enriched Cytotoxic T lymphocytes [62].

Treatment of glioblastoma

Studies have shown the benefit of radiomics analysis in planning surgical procedures, evaluating the dose of radiotherapy, predicting the effective dose of chemotherapeutic agents and stratifying patients who will benefit from therapy. After initiating therapies, radiomics can be used to differentiate mimicking entities like true progression, pseudoprogression and radionecrosis(Table 3).

Surgical resection

A study correlating tumor surface regularity on T1W MRI with OS of 165 glioblastoma patients who underwent surgical resection highlighted that patients with surface-regular tumors had a higher survival rate and benefit from total tumor resection as compared to surface-irregular tumor patients [62]. Gaw et al. created a hybrid model to predict tumor cell invasion preoperatively for more effective surgery and radiation planning. The hybrid model, comprising an ML component that was driven by imaging data and a mechanistic model of tumor growth called the Proliferation-Invasion (PI) model, outperformed the individual components [68]. Thus, radiomics can help plan a targeted and personalized surgical treatment.

Radiation therapy (RT) planning

Radiomics shows immense potential to guide precision radiotherapy. Prediction models can estimate the extent of tumor infiltration and can help identify areas that are at a

Table 3 Application of radiomics in glioblastoma treatment

Authors and reference nos	Year	Study sample (*n*)	Task	Machine learning algorithm	Performance parameter
Akbari et al. [63]	2016	Glioblastoma (65)	Predict subsequent location of recurrence	Support vector machine	AUC 0.84, sensitivity 91%, specificity 93%
Baine et al. [64]	2021	Pre-radiotherapy scans (35)	Predicting Risk of Pseudoprogression	–	AUC 0.82
Bani-Sadr et al. [65]	2019	Glioblastoma patients (76)	Differentiate pseudoprogression from early progression	Random forest	Combined model accuracy 79.2%, specificity 75%
Cai et al. [66]	2020	Patients receiving bevacizum ab (149)	Predicting the response to bevacizumab in brain necrosis after radiotherapy	Logistic regression analysis	AUC 0.912
Elshafeey et al. [67]	2019	gbm patients (98)	Differentiating between pseudoprogression and progressive disease	Support vector machine	Ktrans: AUC = 94%; rCBV: AUC = 89.8%
Gaw et al. [68]	2019	Primary GBM patients (18)	Variation in cell density	Graphbased semisupervised learning algorithm	Hybrid ML-PI model mean absolute predicted error (MAPE) of 0.106
Grossmann et al. [69]	2017	Multicenter BRAIN trial (291)	Stratify survival and progression in patients treated with bevacizumab		–
Kickingereder et al. [47]	2016	Patients recurrent glioblastom a prior to bevacizum ab treatment (172)	Stratify survival in patients treated with bevacizumab	Supervised principal component (superpc) analysis	Radiomic superpc predictor (IBS and iAUC of 0.095 and 0.792 for OS; 0.117 and 0.678 for PFS) was higher
Kim et al. [70]	2019	Glioblastom as within 3 months after standard Treatment (61)	Differentiate pseudoprogression from early tumor progression	Generalized linear model	External validation AUC 0.85; internal Validation AUC 0.96
Pérez-Beteta et al. [62]	2018	Glioblastom a, TCIA (116)	Predicts survival and response to surgery	Cox proportional hazards regression analysis	Discovery: C index 0.76; validation: C index 0.74
Petrova et al. [71]	2019	Patients with recurrent glioblastom a (54)	Response to treatment	Support vector machine	Accuracy 0.78% (OS) 0.82% (PFS6)
Pope et al. [60]	2011	Up-front bevacizum ab-treated + control patients with newly diagnosed GBM (121)	Stratify survival in patients treated with bevacizumab	–	–
Yan et al. [72]	2020	Newly diagnosed cerebral glioblastom a (57)	To identify peritumoural progression areas in patients treated with surgery and concomitant chemoradiotherapy	Convolution al neural network	Training: accuracy 92.6%; validation: accuracy 78.5%. Multimodal MR radiomics
Yoon et al. [73]	2020	GBM patients (118)	Prediction of overall survival after postoperative concurrent chemoradiotherapy	Deep learning/CNN	Combined model Cindex 0.768, iAUC 0.790
Zhang et al. [74]	2018	Pathologically confirmed necrosis or progression (87)	Distinguishing radiation necrosis from tumour progression after gamma knife radiosurgery	RUSBoost ensemble classifier	Overall predictive accuracy 73.2%; AUC 0.73
Patel et al. [75]	2021	Glioblastoma patients (76)	Differentiate between early true progression and Pseudoprogression	Machine learning-based tissue classification	AUC 0.80, sensitivity specificity 78.2, 66.7%, accuracy 73.7%
Rathore et al. [76]	2018	De novo glioblastoma a patients (90)	Predicting recurrence of GBM by estimating peritumoral edema infiltration	Support vector machine	Accuracy 87.51%, sensitivity 80.65%, specificity 87.63%

higher risk of tumor recurrence for targeted RT [63, 76]. Rathore et al. worked on a method for estimating peritumoral edema infiltration using radiomics by testing on pre- and post-operative multimodal MRI sequences in 90 de novo glioblastoma patients and found that recurrent tumor regions revealed higher vascularity and cellularity when compared with the non-recurrent regions [76]. A similar study done on 31 de novo glioblastoma patients confirmed these findings and also highlighted the importance of using multiparametric pattern analysis methods for planning a focused treatment approach to decrease recurrence rate [63]. Radiomics can guide in planning radiation therapy dose escalation in areas with higher risk of tumor recurrence as well as increasing gross total resection. This method can also help prevent dose-related toxicities seen with RT, salvaging the neural tissue at lower risk areas from damage [77].

Chemotherapy with temozolomide (TMZ)

Chemotherapy with TMZ along with adjuvant RT increases median OS [78]. However, TMZ resistance arises due to tumor heterogeneity. Yan et al. confirmed the importance of radiomics analysis in predicting disease progression in 57 glioblastoma patients treated with TMZ post-surgery using structural, diffusion and perfusion MRI. The study found lower ADC, higher FLAIR and hyperintense signals on T1CE in areas with a higher risk of tumor progression [72]. Another study assessed the efficacy of deep-learning based survival-prediction in 118 patients undergoing concurrent chemoradiotherapy with temozolomide post-surgery using features from multimodal MRI.. It highlighted that both clinical and radiomic features should be used hand in hand to predict OS of glioblastoma patients [73]. This reiterates the importance of radiomic models for identification of suitable treatment regimens guided by predicted response.

Therapy with bevacizumab

Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF) used in patients with recurrent glioblastoma. However, variations in genetic makeup of VEGF among individuals can lead to resistance to bevacizumab, limiting its use [47]. Radiomics analysis can provide important biomarkers for selecting patients who will benefit from this therapy. Pre-treatment T1W and T1CE MRI of patients with recurrent glioblastoma were used to develop radiomics-based predictors of survival and progression. This has utility as a low-cost instrument for identifying treatment response in these patients [47, 69]. Using ADC and CBV of 54 patients with recurrent glioblastoma that were treated with RT and temozolomide, and subsequently treated with bevacizumab, was effective in segregating patients into responders and non-responders to bevacizumab treatment [71]. In a more complex model, a stratification model was created which integrated the pre-treatment MRI radiomics signature, the interval between radiotherapy and diagnosis of brain necrosis, and the interval between diagnosis of brain necrosis and treatment with bevacizumab to predict which patients will benefit from bevacizumab therapy for brain necrosis after radiotherapy. This model performed well with an AUC of 0.912 in the validation set [66].

Evaluating response to radiation therapy (RT) and chemotherapy

Radiotherapy can result in conditions that mimic true disease progression. Texture features derived from enhancing component and perilesional edema on structural MRI were used to differentiate pseudoprogression from true progression in glioblastoma [79]. Another model displayed a boost in accuracy when MGMT status was incorporated [65]. While these studies were based on post-RT MRI, pre-RT MRI scans may also predict the development of future pseudoprogression in glioblastoma patients [64]. Recent studies incorporated diffusion and perfusion MRI which reflect hypercellularity and hypervascularity to classify pseudoprogression.the accuracy is superior in these models than those based on conventional MRI alone [70, 67, 80]. Another post-RT effect that is difficult to differentiate from true progression is radiation necrosis. This can also be detected using ML classifiers based on traditional and delta radiomic features derived from MRI [74]. Pseudoprogression can also follow chemotherapy and radiomics offers hope in this regard. A clinio-radiomic classifier including multimodal MRI features was developed which showed an AUC of 0.80 [75].

Challenges in the clinical application of radiomics for glioblastoma

Despite the proven potential of radiomics in various aspects of glioblastoma management, these methods are yet to be introduced in mainstream clinical practice. Obstacles to translation include limited reproducibility of algorithms and less robust machine models. Formation of bodies to recommend standardization methods such as QIBA and QIN offer hope [81, 82].

Data availability and sharing

The majority of the studies exploring radiomics in glioblastoma are limited by small sample sizes. Biological variability of the tumor among patients explains why radiomics is still in its infancy. Promoting collaborative studies, sharing of data across institutions and making more high-quality datasets publicly available (such as Huiyihuiying Inc.,

BraTS, TCGA [83–85]) will result in more robust as well as reproducible models. This also requires overcoming the administrative and regulatory barriers to large-scale data sharing. In addition, clearly documenting the analysis and making original codes and data available will allow other investigators to replicate the results [62].

Image acquisition

The inclusion of retrospectively collected, multi-center data for clinical trials on radiomics is limited by variations across institutions in image acquisition such as the protocol defined by physicians, resolution, slice thickness, and washout period for contrast imaging of the acquired images [86]. Features extracted from MRI images can be influenced by field of view, field strength and slice thickness [87]. To combat the variability in the data collected, standardized steps are recommended following the image acquisition like intensity normalization, voxel re-slicing, use of a specific anatomical plane for multiparametric data, standardization of signal intensity prior to image listing, and developing algorithms for multiple MR modalities for image registration [86, 88, 89].

Segmentation and feature extraction

Although considered the highest standard for segmentation, manual segmentation of images is labor-intensive and increases risk of observer bias. In contrast, semi- and fully-automated methods can improve robustness and reproducibility [90]. Extracted features are dependent on the segmented region and tumor margins therefore segmentation is the key step [87]. While automated feature extraction has lower degree of variation in the scoring of semantic features [86], these methods can still lead to site-specific variations when obtaining imaging [86].

Machine learning models

Accuracy of ML models is limited by overfitting and underfitting. Overfitting of data occurs when doing feature extraction on high-dimensional, large-scale data [83]. However, it can be reduced by feature selection methods such as principal components analysis (PCA), sparse PCA, auto-encoders, etc. [91, 92]. Underfitting, due to small sample sizes, can be addressed using techniques like SMOTE [93].

Conclusion

Radiomics offers revolutionary changes in the scope of glioblastoma management through facilitating a personalized approach at various stages. Integrative models that include clinical, genetic and other molecular data can enhance the accuracy. The main limitation seen in most studies is the small sample size and the retrospective nature of these projects. Besides, variability in methods to generate data across institutions limits the generalizability in different patient populations. Whilst the results of these studies are promising, a key goal moving forward is to make these models more reproducible in a wide array of settings. Multicenter clinical trials are needed to translate these models and provide actual benefits to glioblastoma patients.

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