

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 intra-tumoral 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 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.

Glioblastoma:

Glioblastoma has an incidence of 3.22 per 100,000 and a 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 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.[3,4,5] Personalized treatment protocols targeting individual patient’s 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 (Figure 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. Combining radiomics with clinical and genetic prognostic factors yields superior can result in predicting the survival of patients than using each component alone.

Diagnosis and classification of glioblastoma:

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

Tumor location:

It is well known that 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,[11] supporting their invasive nature and poor prognosis.[12] A comparison between solitary and multicentric glioblastoma revealed distinct gene expression profiling and outcomes between the two types, with upregulation of genes responsible for tumor cell motility and invasiveness in the multicentric type.[13]Another study showed correlation of tumor phenotypes with spatial distribution of tumors.[14]Thus, tumor location provides important information on the cell of origin and tumor behavior.

Tumor size and contrast enhancement patterns:

The volumes of both contrast enhancement and necrosis at the time of initial diagnosis were found higher in tumors with the mesenchymal gene expression signature compared with those having proneural or proliferative signatures. A ratio of the T2/FLAIR hyperintense volume to the volume of contrast enhancement plus necrosis of less than 2.3 could predict the mesenchymal subtype with 82% sensitivity

and 87% specificity.[15] VAK Classification, a scoring system developed to create phenotypes based on tumor Volumetry, Age, KPS annotation, was combined with P53 activation, MGMT promoter methylation and a group of genes and microRNAs in The Cancer Genome Atlas (TCGA) glioblastoma dataset to predict patient survival and facilitate genomics-based personalized therapy for glioblastoma patients. (Figure 2).[16] 'VASARI', a semi-quantitative feature set named was designed to measure tumor size and volumes of components with enhancement, non-enhancement, necrosis and edema, which correlated with survival rates and subtypes.[17] Specific invasive imaging signatures including ependymal involvement, deep white matter tract involvement and enhancement across the midline predicted a decrease in OS, MYC oncogene activation and inhibition of NF-KB inhibitor-alpha.[18] These patients were found to have mitochondrial dysfunction,[18] consistent with the "Warburg effect",[19] where cancer cells rely on aerobic glycolysis facilitated by MYC oncogene upregulation.

Volumetry was combined with DNA microarray analysis to train classifiers that can predict gene-expression patterns and survival. Tumor contrast enhancement and mass effect was associated with up-regulation of specific hypoxia and proliferation gene-expression programs such as VEGF, ADM, PLAUR, SERPINE1, CA12, TOPA, CDC2, and BUB1B.[20] In another radiogenomic study based on TCGA, stratification into high and low FLAIR radio-phenotypes reflected underlying edema and cellular invasion in glioblastoma, as they were associated with genes and microRNAs involved in cancer and cellular migration.[21] 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.[22] These studies provide a basis for genomic profiling and non-invasively selecting patients for personalized therapies using tumor volumetry.

Radiomics was used to distinguish brain metastasis and glioblastoma using contrast-enhancing and peritumoral hyperintense masks in T2-weighted (T2W) MRI. In this model, deep learning 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).[23] Similar performance, AUC 0.96 for support vector machine (SVM), was observed in another study which used post-contrast T1 weighted (T1CE) MRI instead. However, performance decreased when subtypes of brain metastasis were attempted to classify.[24]

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.[25] 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. 26 Other studies on texture features were able to predict MGMT methylation status with reasonable accuracy.[27,28]

Occasionally, high-grade gliomas (WHO Grade III and glioblastoma) may have the same MRI appearance as low-grade gliomas. A radiomic analysis using texture along with size, shape, intensity, and histogram

features was used to differentiate low-grade from high-grade gliomas, reaching a prediction performance in the cross-validation as high as AUC value of 0.932 with support vector machine. However, the accuracy decreased to 0.75 in the independent validation dataset.[29] In a similar study, Random Forest gave the highest AUC in the training cohort compared to test cohort, reflecting variation in accuracy across different ML classifiers.[30]

Advanced MRI sequences and multimodal analyses:

Perfusion MRI has been extensively used in brain tumors to evaluate 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.[31] A Cochrane meta-analysis on 7 studies to differentiate untreated solid and non-enhancing low-grade from 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.[32] 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.[33] In another study, physiologic MRI was correlated with stereotactic image-guided biopsies to differentiate contrast-enhancing and non-enhancing 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 used 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. Accuracy of these results could be confounded by the misregistration arising as a result of brain shift.[34]

MR imaging features of Primary CNS Lymphoma (PCNSL) and glioblastoma overlap, with differing survival outcomes and treatment options. In one study, 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.³⁵ In another study, ADC was outperformed by a multi-parametric (T1-weighted post contrast T1WCE, post-contrast T2Wand T2 FLAIR) and multiregional radiomics classifier with AUC 0.921.[36]

Studies have used multiparametric MRI to create more accurate radiomic models for tumor subtyping. Rathore et al. used 267 multiparametric MRI based radiomic features, extracted from T1-weighted (T1W), T2W, T1WCE, T2 FLAIR, DSC, and DTI to train classifiers 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.[14] combining various MRI sequences can improve classification accuracy for tumor grading. 37,38 Accuracy also increased using MRI features from multiregional and multiparametric structural MRI to predict MGMT methylation status in glioblastoma.[39,40] Similarly, IDH 1 mutation status was predicted using radiomic features on multiparametric MRI with enhanced accuracy when age and multiple regions were included.[41]

Prognostication of Glioblastoma:

It is increasingly important for physicians to understand an individual patient's prognosis and adjust their therapy accordingly. Radiomics alone and augmented with clinical data, genomics, and proteomics can be used to predict outcomes (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 on T1W MRI.[42] 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).[43] Similar combined models reached C-index of 0.974.[44]

Texture, tumor shape and volumetric features were extracted, and combined with patient age to produce a model that would predict short-term, mid-term, and long-term OS.[44,45] 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.[46] Similarly, Chaddad et al found three texture features extracted from active part of the tumors that significantly predicted survival outcomes compared to necrotic and edematous parts. [25] Moreover, these radiomic models could predict survival in different molecular subtypes as well.[47]

Advanced MRI features:

Advanced MRI modalities have also been explored to predict glioblastoma patient outcomes.[48] It was seen that high rCBV in the non-enhancing region of tumor was predictive of worsening OS and Progression-free Survival (PFS).[49] Pre-treatment ADC histogram analysis was useful to predict PFS in bevacizumab-treated patients with newly diagnosed as well as recurrent glioblastoma.^{33,50} In these studies, low ADC predicted poor outcomes.

Radiogenomics and proteomics:

MGMT promoter hypermethylation, associated with better prognosis and response to therapy, has been combined with radiomic features from structural MRI to stratify patients based on overall survival.

Adding MGMT and IDH1 mutation status resulted in more robust radiomics-based prognostic models. [51,52] 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.[16] In another study, glioblastomas were 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).[53] Other studies did not find any significant association of prognosis with MGMT promoter hypermethylation.[42,54] This could be due to insufficient feature selection methods.

Integrative models promise a reduction in prediction errors.[51,55] 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%.[56] Liao et al. us extracted First order and multi-dimensional features from segmented lesions on T2-FLAIR MRI and gave a feature importance score for feature selection.[57] When combined with genetic expression, the Gradient Boosting Decision Tree model gave a 0.81 accurate prediction of both short-term and long-term survival. Six metagenes showed significant interactive effects with image features. However, this study was limited by unavailability of complete genomic data.[57]

Immunophenotypes in glioblastoma are important as they predict response to immunotherapy and outcomes. Hsu et al. used radiomic immunophenotyping models to predict patient prognosis.[58] The phenotype with the worst prognosis comprised highly enriched myeloid-derived suppressor cells and lowly enriched Cytotoxic T lymphocytes.[58]

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 recent study examined the correlation of tumor surface regularity on T1W MRI and OS of 165 glioblastoma patients who underwent surgical resection and 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.[59] Gaw et al used machine learning models to better predict tumor cell invasion before resection was conducted.[60] Their aim was to allow for more effective surgery and radiation planning and created a hybrid model with Proliferation-Invasion (PI) model of glioma growth and pre-operative MRIs.[60] 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 higher risk of tumor recurrence for targeted RT.[14,61] 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.[14] 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.[61] Thus, 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.[62]

Chemotherapy with Temozolomide (TMZ):

Chemotherapy with TMZ along with adjuvant RT increases median OS.[63] 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 MR. The study found lower ADC, higher FLAIR and contrast enhanced T1 signals in areas with a higher risk of tumor progression.[64] In another study assessing the efficacy of using a deep-learning based survival-prediction model of 118 patients undergoing concurrent chemoradiotherapy with temozolomide post-surgery, radiomics features including T1W with and without contrast, T2 FLAIR and ADC images were used to assess the OS. While there was no difference observed between the two groups, it highlighted that both clinical and radiomic features should be used hand in hand to predict OS of glioblastoma patients.[65] This reiterates the importance of radiomic models predictive of treatment response to identify suitable treatment regimens.

Therapy with Bevacizumab:

However, variations in genetic makeup of VEGF among individuals can lead to resistance to bevacizumab and limiting its use.[66] Radiomics analysis can provide important biomarkers for selecting patients and to predict the treatment outcome. T1W and T1WCE MRI of 172 patients with recurrent glioblastoma prior to treatment with bevacizumab were used to develop radiomics-based survival predictor as a low-cost instrument for identifying treatment response in these patients.[66] In patients with recurrent glioblastoma receiving bevacizumab treatment, radiomics features from T1WCE obtained at baseline and post-treatment showed prognostic value for survival and progression.[67] 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.[68] To predict which patients will benefit from bevacizumab therapy for brain necrosis after radiotherapy, 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. This model achieved AUC 0.912 in the validation set.[69]

Evaluating response to Radiation Therapy (RT):

Texture features derived from enhancing component and peri-lesional edema on structural MRI were used to differentiate pseudoprogression from true progression in glioblastoma.[70] Another model achieved high sensitivity and moderate specificity; incorporating the MGMT status further increased accuracy.[71] While these studies were based on post-RT MRI, pre-RT MRI scans to predict the development of future pseudoprogression in glioblastoma patients gave an AUC of 0.82.[72] Recent studies show that incorporating diffusion and perfusion-weighted MRI, which reflect hypercellularity and hypervascularity of tumor, improves the accuracy in detecting pseudoprogression than conventional MRI alone.[73-75]

Radiation necrosis, another post-RT effect that is difficult to differentiate from true progression, can be detected using ML classifiers based on traditional and delta radiomic features derived from MRI.[76]

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.[77,78]

Data availability and sharing:

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 infancy. Promoting collaborative studies, sharing of data across institutions and making more high-quality datasets publicly available (such as Huiyihuiying Inc., BraTS, TCGA[79-81]) 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.[59]

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.[82] Features extracted from MRI images can be influenced by field of view, field strength and slice thickness.[83] 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.[82,84,85]

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.[86] Extracted features are dependent on the segmented region and tumor margins therefore segmentation is the key step.[83] While automated feature extraction has lower degree of variation in the scoring of semantic features,[82]these methods can still lead to site-specific variations when obtaining imaging.[82]

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.[79] However, it can be reduced by feature selection methods such as principal components analysis (PCA), sparse PCA, auto-encoders, etc. [87,88]Underfitting, due to small sample sizes, can be addressed using techniques like SMOTE.[89]

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 benefit to glioblastoma patients.

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Tables

Table 1. Application of radiomics in glioblastoma diagnosis and classification

Authors	Year	Study Sample (n)	Task	Machine Learning Algorithm	Performance parameter
Artzi et al.	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.	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.	2012	newly diagnosed glioblastoma (51)	histopathologic correlation of MRI features	mixed effect models	
Cho et al.	2018	High grade and low grade gliomas, BraTS 2017 (285)	glioma grading	Random Forest	AUC 0.9213
Colen et al.	2014	treatment-naïve glioblastoma, TCIA (104)	radiogenomics in invasive phenotype	Robust Multi-Array (RMA)	
Drabycz et al.	2010	newly diagnosed GBM (59)	predicting MGMT methylation status	bicubic interpolating kernel	accuracy 71%
Ellingson et al.	2013	de novo glioblastoma (507)	probabilistic radiographic atlases (tumor locations indicative of cells of origin)	mutual information algorithm / ADIFFI analysis	
Gutman et al.	2015	glioblastoma, TCIA (76)	predicting somatic mutations		AUC 0.646 - 0.722
Jeong et al.	2019	high-grade and low-grade gliomas (25)	glioma grading	random forest	Accuracy 0.950 HG and 0.850 for LG; AUC 0.94.
Hajianfar G et al.	2019	glioblastoma with known MGMT methylation status (82)	predicting MGMT methylation status	Decision Tree classifier	AUC 0.78

Korfiatis P et al.	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.	2016	treatment-naïve GBM (51)	phenotyping multicentric GBM	shortest path algorithm	
Lee et al.	2015	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.	2018	glioblastoma (133 training, 60 validation cohort) (193)	predicting MGMT methylation status	random forest	AUC=0.88, accuracy=80 % Radiomics model
Lin et al.	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.	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.	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.	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.	2012	newly diagnosed glioblastoma Up-front bevacizumab-treated (38)	tumor stratification (gene expression in high-versus-low ADC tumors)	Positive Pixel Count and Nuclear Algorithms	
Rathore et al.	2018	de novo glioblastoma (261)	imaging based phenotypes for risk-stratification	support vector machine	accuracy 80.19% within subtypes, 73.58% across all patients
Sasaki et al.	2019	newly diagnosed	predicting MGMT status	LASSO	Accuracy 67%, Sensitivity 67%, Specificity 66%, Positive predictive value

		GBM patients (201)			67%, Negative predictive value 67%, Prevalence of pMGMT methylation 50%
Tian et al.	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.	2018	GBM patients (98)	predicting MGMT methylation status	support vector machine	Training: accuracy 86.59% validation: accuracy 80%.
Zhang et al.	2017	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.	2017	High grade and low grade gliomas (120)	glioma grading	support vector machine	Accuracy 0.945
Zinn et al.	2012	glioblastoma, TCIA (142)	patients stratification		
Zinn et al.	2011	glioblastoma, TCIA (78)	Radiogenomic Mapping of Edema/Cellular Invasion	Ingenuity Pathway Analysis (IPA).	

Table 2. Application of radiomics in glioblastoma survival prediction

Authors	Year	Study Sample (n)	Predictors of survival	Machine Learning Algorithm	Performance parameter
Beig et al.	2018	glioblastoma (115)	radiomics features+ expression profile of 21 hypoxia-associated genes	Random forest and information gain	combined C-index = 0.69 training set, 0.83 on validation set
Choi et al.	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.	2016	glioblastoma, TCIA (40)	radiomics	decision trees (DT)	accuracy 79.31, sensitivity 91.67, and specificity 98.75 %
Diehn et al.	2008	glioblastoma (25)	radiomics (predictive of gene-expression pattern)	two-step algorithm	-
Fuster-Garcia et al.	2021	NCT03439332 clinical study (96)	MGMT methylation and rCBV	cox regression	AUC 0.70 for MGMT
Gutman et al.	2013	glioblastoma, TCIA (75)	Radiomics (predictive of molecular profile)	Cox regression	-
Hsu et al.	2020	glioblastoma (116)	radiomics features predicitive of immunophenotypes	Random forest and information gain	accuracy 79%
Kickingereeder et al.	2018	newly diagnosed glioblastoma (181)	Radiomics + Clinical + Molecular	Cox regression	prediction error reduced by 36% for PFS and 37% for OS
Jain et al.	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.	2017	glioblastoma (112)	radiomics features + clinical factors	pre-trained CNN via transfer learning/ deep learning	combined model C-index = 0.739
Liao et al.	2019	glioblastoma, TCIA (137)	Radiomics (predictive of gene-	Gradient Boosting	accuracy 0.81, AUC of the short and long

			expression patterns)	Decision Tree	survival time class 0.79 and 0.81.
Molitoris et al.	2017	supratentorial GBM initiated TMZ-based concurrent chemotherapy	age, gender, MGMT status, performance status, resection extent, race, tumor site	Cox regression	-
Park et al.	2020	newly diagnosed glioblastoma (216)	multiparametric MR prognostic model (radiomics score + clinical predictors)	Cox regression	C-index 0.74
Sanghani et al.	2018	GBM patients from the BraTS 2017 dataset (163)	Radiomics	Support vector machine classification	accuracy 97.5%
Sasaki et al.	2019	newly diagnosed GBM (201)	Radiomics + MGMT status	Supervised principal component analysis (SPCA)	
Tixier et al.	2019	GBM (159)	Radiomics + MGMT status	-	
Yang et al.	2015	de novo GBM (82)	radiomics	random forest	AUC 0.69 for 12-month survival status
Zhang et al.	2019	GBM (105)	radiomics + clinical	Logistic regression	training: C-index, 0.971, validation: C-index 0.974
Zhou et al.	2017	glioblastoma (54)	image-based spatial characteristics in tumor subregions	Support Vector Machine	accuracy 87.50% (dataset 1) 86.36% (dataset 2)

Table 3. Application of radiomics in glioblastoma treatment

Authors	Year	Study Sample (n)	Task	Machine Learning Algorithm	Performance parameter
Akbari et al.	2016	gbm (65)	Predict Subsequent Location of Recurrence	Support Vector Machine	AUC 0.84, sensitivity 91%, specificity 93%.
Baine et al.	2021	pre-radiotherapy scans (35)	Predicting Risk of Pseudoprogression	-	AUC 0.82
Bani-Sadr et al.	2019	gbm patients (76)	differentiate pseudoprogression from early progression	random forest	Combined model accuracy 79.2%, specificity 75%
Cai et al.	2020	patients receiving bevacizumab (149)	Predicting the Response to Bevacizumab in Brain Necrosis after Radiotherapy	logistic regression analysis	AUC 0.912
Elshafeey et al.	2019	gbm patients (98)	differentiating between pseudoprogression and progressive disease	Support Vector Machine	Ktrans: AUC = 94% ; rCBV: AUC = 89.8%
Gaw et al.	2019	primary GBM patients (18)	variation in cell density	graph-based semi-supervised learning algorithm	hybrid ML-PI model mean absolute predicted error (MAPE) of 0.106
Grossmann et al.	2017	multicenter BRAIN trial (291)	stratify survival and progression in patients treated with bevacizumab		-
Kickingereeder et al.	2016	patients recurrent glioblastoma prior to bevacizumab 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.	2019	glioblastomas 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.	2018	glioblastoma, 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.	2019	patients with recurrent glioblastoma (54)	Response to treatment	support vector machine	Accuracy 0.78% (OS) 0.82 % (PFS6)
Pope et al.	2011	Up-front bevacizumab-treated + control patients with newly diagnosed GBM (121)	stratify survival in patients treated with bevacizumab	-	-
Yan et al.	2020	newly diagnosed cerebral glioblastoma (57)	to identify peritumoural progression areas in patients treated with surgery and concomitant chemoradiotherapy	convolutional neural network	training: accuracy 92.6%; validation: accuracy 78.5%. Multimodal MR radiomics
Yoon et al.	2020	GBM patients (118)	Prediction of Overall Survival after Postoperative Concurrent Chemoradiotherapy	deep learning/CNN	combined model C-index 0.768 , iAUC 0.790
Zhang et al.	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.

Figures

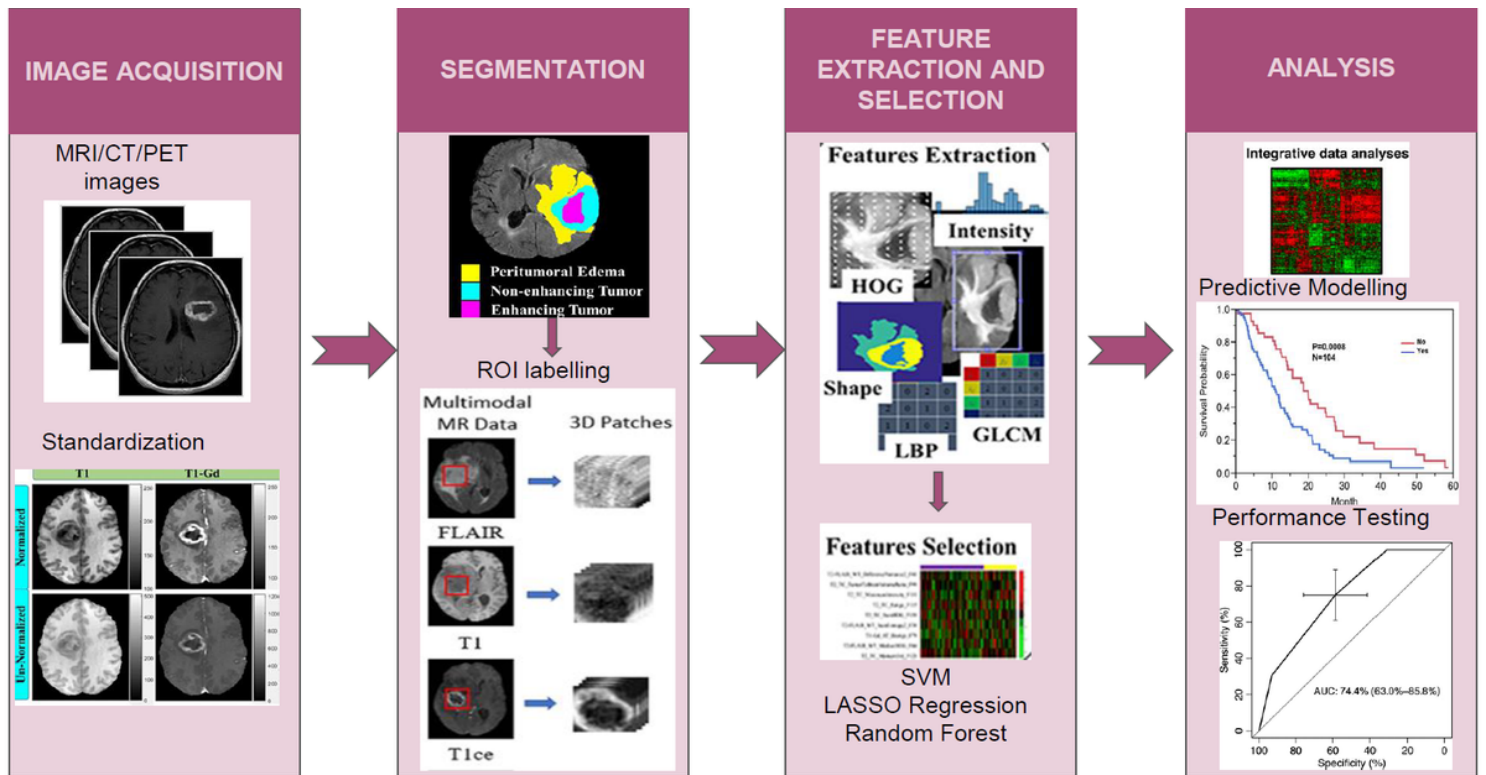


Figure 1

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.

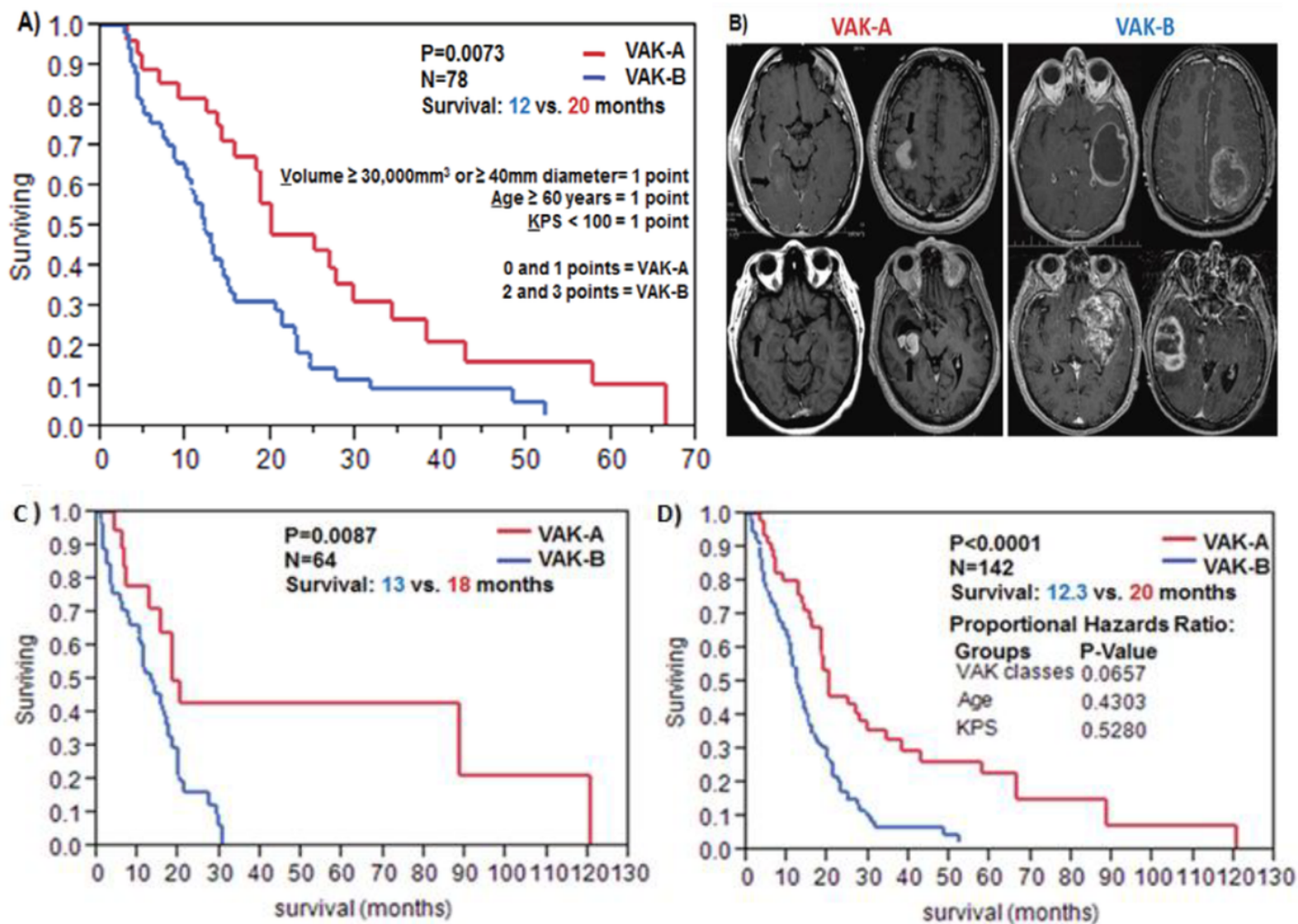


Figure 2

Volume, Age, KPS (VAK) classification and phenotype. Volume, Age, KPS (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>