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Radiomic Texture Feature Descriptor to Distinguish Recurrent Brain Tumor from Radiation Necrosis using Multimodal MRI

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ABSTRACT

Despite multimodal aggressive treatment with chemo-radiation-therapy, and surgical resection, Glioblastoma Multiforme (GBM) may recur which is known as recurrent brain tumor (rBT). There are several instances where benign and malignant pathologies might appear very similar on radiographic imaging. One such illustration is radiation necrosis (RN) (a moderately benign impact of radiation treatment) which are visually almost indistinguishable from rBT on structural magnetic resonance imaging (MRI). There is hence a need for identification of reliable non-invasive quantitative measurements on routinely acquired brain MRI scans: pre-contrast T1-weighted (T1), post-contrast T1-weighted (T1Gd), T2-weighted (T2), and T2 Fluid Attenuated Inversion Recovery (FLAIR) that can accurately distinguish rBT from RN. In this work, sophisticated radiomic texture features are used to distinguish rBT from RN on multimodal MRI for disease characterization. First, stochastic multiresolution radiomic descriptor that captures voxel-level textural and structural heterogeneity as well as intensity and histogram features are extracted. Subsequently, these features are used in a machine learning setting to characterize the rBT from RN from four sequences of the MRI with 155 imaging slices for 30 GBM cases (12 RN, 18 rBT). To reduce the bias in accuracy estimation our model is implemented using Leave-one-out cross-validation (LOOCV) and stratified 5-fold cross-validation with a Random Forest classifier. Our model offers mean accuracy of 0.967 ± 0.180 for LOOCV and 0.933 ± 0.082 for stratified 5-fold cross-validation using multiresolution texture features for discrimination of rBT from RN in this study. Our findings suggest that sophisticated texture feature may offer better discrimination between rBT and RN in MRI compared to other works in the literature.

Keywords: Recurrent brain tumor, radiation necrosis, radiomics features, multimodal magnetic resonance imaging

1. INTRODUCTION

High-grade gliomas with grade III and IV according to the World Health Organization (WHO) [1,2] is the most aggressive and severe malignant brain tumors. Distinguishing disease phenotypes that have similar morphologic appearances is one of the most challenging problems on neuroimaging. The certain pathologies which appear very similar on imaging exhibit distinct morphological and architectural characteristics on histology. Disease confirmation obtaining from biopsy samples is not always ideal, and the patients end up undergoing complete resection. This often results in morbidity and, at times, mortality. Hence, it is important to develop non-invasive imaging biomarkers to differentiate these conditions reliably and robustly. Which is the basis for subsequent clinical steps and supportive for improving the treatment possibilities of the disease.

Our previous works demonstrated the utility of multiresolution texture features and other hand-crafted imaging features in the context of problem involving brain tumors. In the first application, we proposed an automated model for LGG prediction progression. These different hand-crafted features including structural multiresolution texture are used with a gradient boosting-based regression technique known as gradient boosting (XGBoost) to assess the predictive performance of the LGG progression model. Our proposed method had shown the efficacy of using non-invasive structural MRI to predict the progression of LGG with an AUC of 0.81 ± 0.03 [3]. The second application involves identifying glioma grading and prediction for IDH, ATRX and 1p/19q codeletion mutations using a novel radiogenomics-NB model. The proposed radiogenomics-NB model significantly outperforms compared to the competing models in the literature [4].

An automatic disease phenotypes prediction is a difficult task, as it needs to represent nonlinear relationships between the deep imaging features and histological formation. In addition, the robustness in performance remains an open and difficult challenge in machine learning based models. Recent work developed a new intensity radiomic feature that allows the

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capture of spatial intra-tumoral heterogeneity on a per-voxel basis by capturing local variations in gradient orientations [5-7]. They showed the benefit of this specific class of radiomic features in the context of treatment evaluation in brain tumors – distinguishing treatment confounders from true tumor progression.

The specificity of disease diagnosis has improved considerably with the emergence of newer and faster imaging techniques. Although existing mechanisms and methods provide important information on cancer phenotypes, in many cases the details are not definitive. There are several instances where benign and malignant pathologies might appear very similar on radiographic imaging. One such illustration is radiation necrosis (RN) (a moderately benign impact of radiation treatment) and recurrent brain tumors (rBT), which are visually almost indistinguishable on ordinary MRI [8]; even though both RN and rBT have distinct cellular and architectural arrangements when examined on a pathology slide under a microscope. However, conventional MRI images contain relevant information embedded that can provide insights into the underlying biology. There's, subsequently, a require for recognizing non-invasive markers that can dependably recognize such similar appearing pathologies on routine imaging for early determination as well as treatment assessment. Identification of these imaging biomarkers could possibly forestall the require for unnecessary surgical interventions, as well as exposure to unnecessary radiation, for disease confirmation.

In this study, we propose a novel radiomics model based on selected radiomics/volumetric features which characterize tumor volume and sub-regions in differentiating in recurrent GBM from RN. The purpose of this study was to establish a high-performing radiomics strategy with machine learning from conventional MRI to differentiate recurrent glioblastoma (GBM) from radiation necrosis (RN) after concurrent chemoradiotherapy (CCRT) or radiotherapy (RT).

2. METHODOLOGY

This study proposes a model to discriminate rBT from RN based on multiresolution texture features and other imaging features. Each of the patient in the dataset consists of four modalities of MRI scans and each of the modality have 155 imaging slices. The features are extracted from raw MRI of the tumor volume and different representations the MRI. A feature selection method LASSO is used to select the most significant feature sets. Then, the final model is implemented using LOOCV and Stratified 5- Fold with Random Forest classifier to distinguish rBT from RN on multimodal MRI. Figure 1 illustrates the complete flow diagram of the prediction model of rBT from RN.

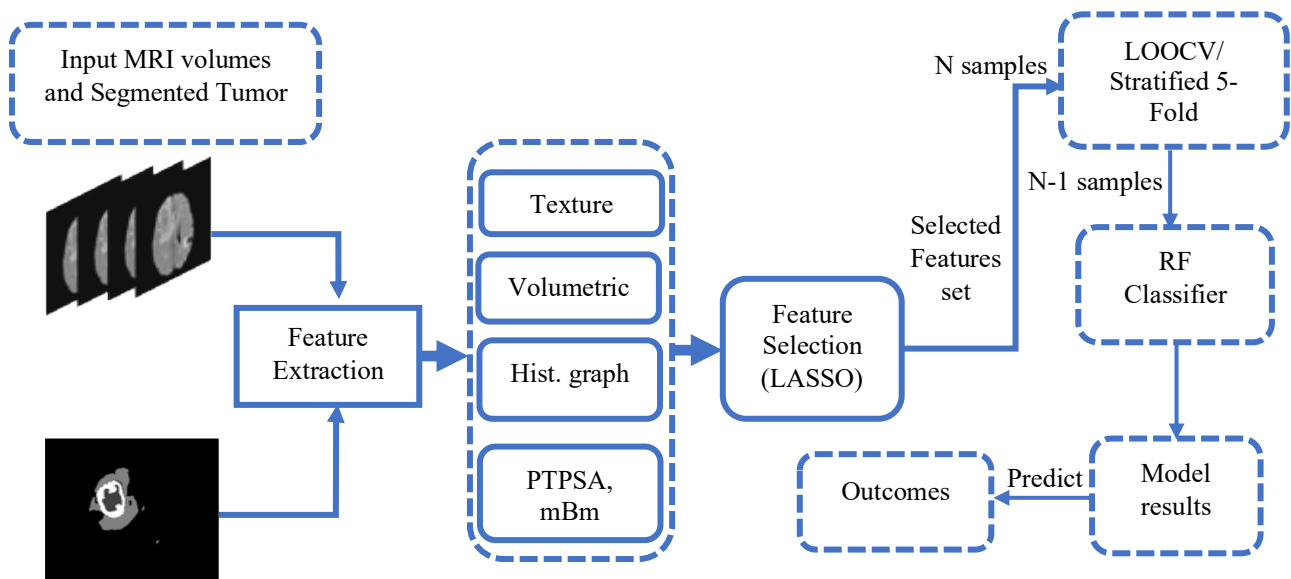


Figure 1. Overall pipeline for recurrent brain tumor classification using Radiomics features. LASSO denotes Least Absolute Shrinkage and Selection Operator. LOOCV denote Leave-one-out cross-validation. N is the number of samples in the dataset

2.1 Dataset

Our proposed method is evaluated on routine multimodal MRI sequences from The Cancer Genome Atlas (TCGA) dataset in the Genomic Data Commons (GDC) Data Portal [9], The Cancer Imaging Archive (TCIA) [10-14] and in an Institutional Review Board-approved (Eastern Virginia Medical School (EVMS) IRB# 20-6-NH-0130), joint study from collaborating institutions: EVMS, Sentara Healthcare and Old Dominion University (Vision Lab). The Clinicopathologic Features of Brain Tumor studies (RN vs rBT) is summarized in Table 1.

Table 1: Clinicopathologic Features of Brain Tumor studies (RN vs rBT)

Number of Patients (samples)	Gender	Age (y, range)
Primary Brain tumors (12RN,18rBT)	13F, 17M	(32-80)

Among the 30 cases, 18 recurrent brain tumor cases are confirmed disease phenotypes (recurrent glioblastoma) and are obtained from TCGA dataset in the GDC Data Portal (<https://portal.gdc.cancer.gov/>) and TCIA [10-12]. For the radiation necrosis cases, we consider multiple factors including tumor resection followed by standard CCRT or RT with adequate clinical radiology follow-up. The radiation-induced necrosis describes a focal lesion in the brain that may occur secondary to any technique of radiation therapy. The radiation necrosis tends to occur later in the course, usually beyond 1 year after radiation [13-15]. We consider the criteria for RN if the contrast-enhancing lesions gradually decrease on more than two subsequent follow-up MRI studies performed at 2–3 month intervals (with a size criterion of a decrease of < 25% of the size of a measurable [< 1 cm] enhancing lesion according to the sum of the products of perpendicular dimensions) and clinical symptoms improved during the follow-up period [16,17]. The sources and the distribution for all 30 GBM cases (12 RN, 18 rBT) are listed in Table 2.

Table 2: Data Sources for Brain Tumor studies (RN vs rBT)

Data Source	# Recurrent Brain Tumor (rBT)	# Radiation Necrosis (RN)
TCGA (GDC)	12	3
TCIA	6	5
SENTARA (EVMS)	-	4
Total	18	12

2.2 Image Preprocessing:

Four sequences of the MRI are provided with the dataset: (T1w, Gd-T1w, T2w, and FLAIR). We performed the image preprocessing steps for each of the scans:

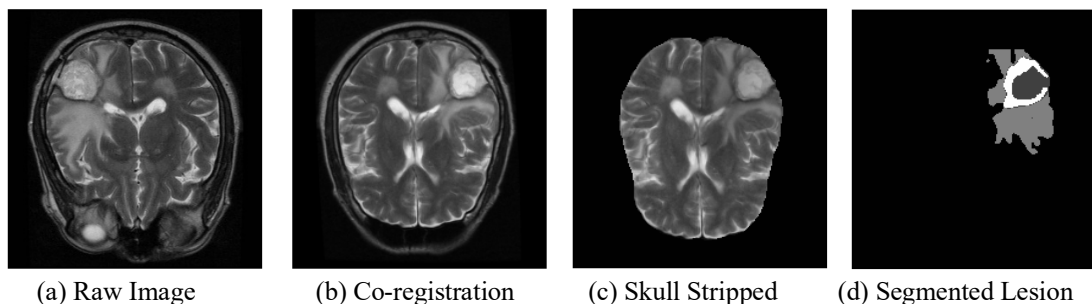


Figure 2. Image Preprocessing Steps

- co-registered to the T1 template,
- re-sampled to 1 mm^3 resolution,
- skull stripping,
- used our 3D deep learning model to have the segmented sub-regions which are verified by the radiologist.

2.3 Feature Extraction:

Radiomics involves computerized extraction of quantitative features from radiographic imaging (i.e., MRI), and provides an opportunity to uniquely capture ‘sub-visual’ identification. While characterizing GBM tumors for predicting survival and treatment response [18-21], a few approaches have recently explored the role of routine texture radiomics (e.g., Haralick), none of these strategies have detailed adequate segregation for clinical appropriateness, nor are domain-inspired. Prateek Prasanna, et al., they developed a new class of radiomic descriptor that can uniquely characterize brain tumor behavior, such as capturing the extent of intra-tumoral heterogeneity, the effect of tumor infiltration to peritumoral regions, and consequences of mass-effect on surrounding healthy parenchyma; characteristics that are related to affected person prognosis and response to treatment. In the following section, we discuss about the implementation of our method. For comparison, we implement a state-of-the-art method in the literature known as the Co-occurrence of Local Anisotropic Gradient orientations (CoLIAGe) features [6,7]. CoLIAGe can capture microarchitecture textural differences in local intensity gradient variations. Particularly, CoLIAGe endeavors to capture neighborhood heterogeneity and disorder in a lesion; mathematically this is often comparable to the entropy feature determined from the co-occurrence of voxel-level gradient orientations.

Texture features are extracted from the whole tumors (WT) and sub-regions (ET, ED, NCR) volume of the T1, Gd-T1w, T2, and FLAIR MRI sequences, which include the histogram-based statistics and matrix-based features (co-occurrence matrix, the neighborhood gray tone difference matrix, and the Size Zone Matrix). Furthermore, histogram-based statistics features are extracted from the different tumor sub-regions (edema, enhance tumor, and necrosis) of the T1, Gd-T1w, T2, and FLAIR MRI sequences. In addition, we extract different volumetric features that describe the volumes of the different sub-regions (ET, ED, NCR). Finally, nine area properties (area, centroid, perimeter, major axis length, minor axis length, eccentricity, orientation, solidity, and extent) are extracted from the whole tumor volume and from three viewpoints (x, y, and z-axes). Furthermore, we extract these texture features from a fractal and multi-resolution fractal representation of the tumor volume. The fractal and multi-resolution fractal representations are piecewise-triangular-prism-surface-area (PTPSA) [22], multifractional Brownian motion (mBm) [23], and Holder exponent (HE) [24,25] of the tumor volume of the four modalities.

In our study, the majority of significant radiomics features from the radiomics model were various second-order features, suggesting that high-throughput characteristics can provide more accurate assessment. The hypothesis for this observation is that second-order features capture the spatial variation in signal intensity, which tend to extract information that may be incomprehensible and invisible to the naked eye. Recent studies have demonstrated that second-order features also reflect the underlying histology. However, a future study with histopathologic correlation is mandatory to prove our hypothesis of the direct relationship between radiomic features in recurrent GBM and RN.

To reduce the biased estimate of the accuracy computed on the dataset our model is implemented using Leave-one-out cross-validation (LOOCV) and Stratified 5-Fold cross-validation. We computed feature matrix from ROI on brain tumor cohorts. A feature selection (LASSO) method is utilized to reduce the high dimensionality of the feature matrix. Then, the features are ranked based on their importance, and the least important features are removed. The selected features are used in a machine learning setting (RF classifier) to characterize the recurrent brain tumor radiation necrosis

3. EXPERIMENTAL RESULTS

We evaluated our model at two levels to distinguish recurrent brain tumor: CoLIAGe feature-based and Texture, Volumetric and Histogram feature -based. For both methods, we use conventional machine learning based method to extract texture features, such as gray level co-occurrence matrix (GLCM). After feature extraction, feature selection is applied, then followed by classifier to distinguish rBT from RN.

Additionally, in order to reduce the high dimensionality of the features in classification steps, we modify both models as follows: 1) calculate and rank the feature importance for each classification; 2) train the modified selected features utilizing RF classifier. As we have a very limited cases, we used Leave-one-out cross-validation which is a special case of cross

validation where the number of folds equals the number of instances in the dataset [26]. Moreover, to avoid overfitting in model performance, Stratified 5-Fold cross-validation is performed. Statistical results across CoLIAGe and other Texture features were compared by computing Precision, Specificity (Recall), f1 score and accuracy, which shown in Figure 3.

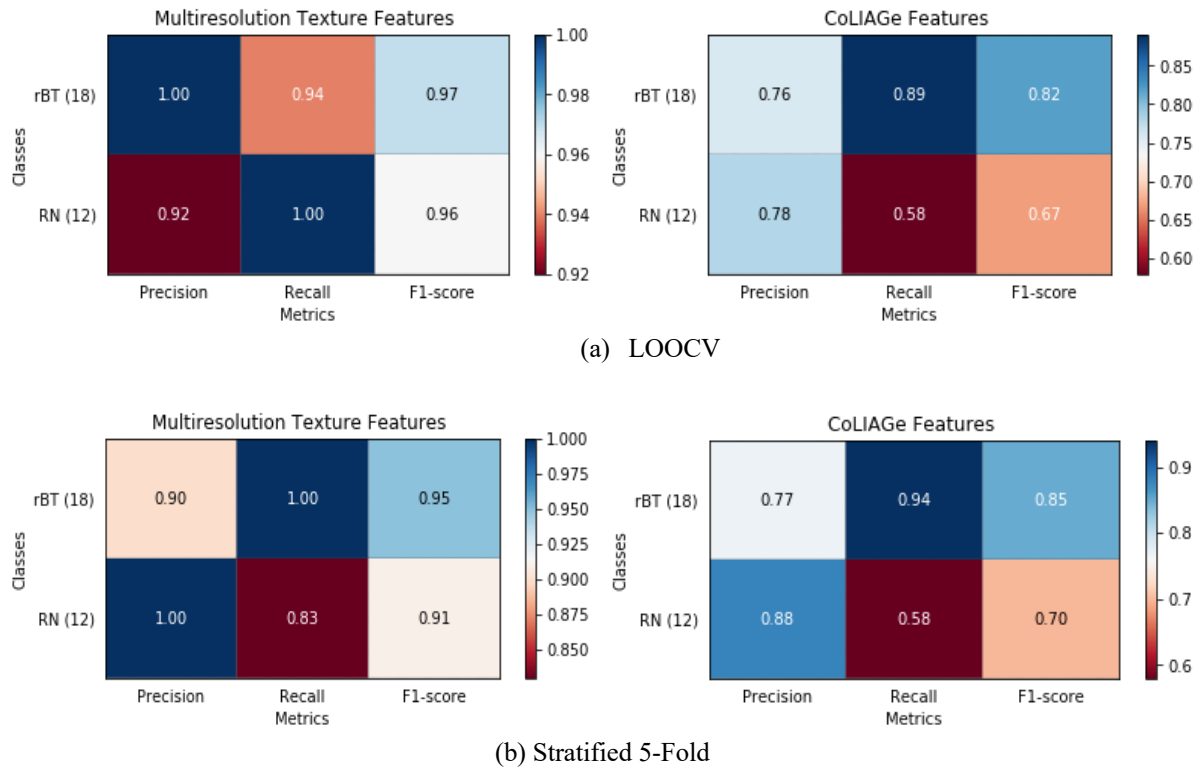


Figure 3. rBT Vs RN Classification report using Multiresolution Texture features and CoLIAGe features: (a) LOOCV, (b) Stratified 5-Fold

We use the similar type of datasets as (Prateek Prasanna, et al.) [6]. The performance comparison shows promising performance by using Texture, Volumetric and Histogram feature method which provides a higher accuracy. The following Table 3 shows the performance comparison of LOOCV and Stratified 5-Fold cross-validation for both Mutireolution texture Features and CoLIAGe features.

Table 3. Performance of Classifier with (a) Texture, Volumetric and Histogram feature and (b) CoLIAGe features

Comparison of Features	Evaluation Method	precision_mean	Specificity_mean	f1_score_mean	Accuracy_mean \pm Std
Texture, Volumetric and Histogram feature	LOOCV	0.97	0.97	0.97	0.967 ± 0.180
	Stratified 5-Fold	0.94	0.93	0.93	0.933 ± 0.082
CoLIAGe	LOOCV	0.77	0.77	0.76	0.770 ± 0.423
	Stratified 5-Fold	0.81	0.80	0.79	0.800 ± 0.125
CoLIAGe (Prateek Prasanna, et al.) [6]	3-fold randomized cross-validation	-	-	-	0.837 ± 0.0543

4. DISCUSSION AND CONCLUSION

In this paper, we use different radiomics and hand-crafted texture features to distinguish recurrent brain tumor from radiation necrosis on multimodal MRI. Moreover, we use feature selection to reduce the high dimensional feature matrix and rank the important features. The best cross-validation accuracy using LOOCV is 96.7% for texture, volumetric and histogram features, while that using 5-fold validation is 80.0% for CoLIAGe feature, respectively. The performance of the proposed method suggests that sophisticated texture feature may offer better discrimination between rBT and RN in MRI compared to other comparable methods in the literature. In future, we plan to distinguish tumor recurrence and pseudo progression by utilizing radiomics features.

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