DYNAMIC CO-OCCURRENCE OF LOCAL ANISOTROPIC GRADIENT ORIENTATIONS (DYCOLLAGE) DESCRIPTORS FROM PRE-TREATMENT PERFUSION DSC-MRI TO PREDICT OVERALL SURVIVAL IN GLIOBLASTOMA

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Abstract

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A significant clinical challenge in glioblastoma is to risk-stratify patients for clinical trials, preferably using MRI scans. Radiomics involves mining of sub-visual features that could serve as surrogate markers of tumor heterogeneity from routine imaging. Previously our group had developed a new gradient-based radiomic descriptor, Co-occurrence of Local Anisotropic Gradient Orientations (COLLAGE), to capture tumor heterogeneity on structural MRI. I present an extension of CoLLAGE on perfusion MRI, termed dynamic COLLAGE (DyCoLIAGe), and demonstrate its application in predicting overall survival in glioblastoma. Following manual segmentation, 52 CoLIAGe features were extracted from edema and enhancing tumor at different time phases during contrast administration of perfusion MRI. Each feature was separately plotted across different time-points, and a 3rd-order polynomial was fit to each feature curve. The corresponding polynomial coefficients were evaluated in terms of their prognosis performance. My results suggest that DyCoLIAGe may be prognostic of overall survival in glioblastoma.

1 Introduction

Glioblastoma is the most common malignant primary brain tumor in adults with a median survival time ranging from 12-14 months. Prognosis outcome for GBM patients vary substantially, with less than 5% of patients surviving for more than 5 years[1]. With new experimental clinical trials becoming available, there is a need to identify patients who may have poor prognosis and may be at high-risk of experiencing conventional treatment failure, so they could be recruited in alternate experimental treatments. While KPS, IDH, and MGMT mutations have shown promise, currently there do not exist any clinically validated biomarkers to predict patient survival in Glioblastoma. There is hence a need for identifying markers that can predict overall survival in Glioblastoma.

Imaging plays an important role in disease diagnosis, outcome prediction and treatment evaluation because it contains information that reflects the underlying pathophysiology of the disease. For instance, structural MRI (T1w, T1-Gd contrast, T2w, FLAIR) provide structural information regarding the lesion location, level of tissue involvement, and resultant mass effect upon the brain[2]. Diffusion weighted imaging utilizes apparent diffusion coefficient (ADC) to identify early ischemic stroke.

Dynamic susceptibility contrast (DSC) perfusion imaging is a T2* weighted imaging technique which utilizes reduction of local susceptibility caused by injection of a paramagnetic contrast agent. A signal intensity time curve is obtained and perfusion metrics regarding blood flow of tissue are derived from the signal intensity time curve. Perfusion imaging is based on the rationale that malignant tumors tend to have higher

level of neovascularization compared to benign tumors, thus affecting amount of contrast agent absorbed and the intrinsic tissue T2/T2* signal on the perfusion images. Previous studies have shown that perfusion parameters using maximum relative cerebral blood volume ($rCBV_{max}$)[3] and maximum relative cerebral blood flow ($rCBF_{max}$)[4] computed from the signal intensive time curves, have the potential to predict glioblastoma patients' overall survival. Histogram analysis of perfusion parameters has also been found to be a useful method for survival prediction. Romano, A. et al have used rCBV histograms generated from the solid portions of the tumor and the mean, median, kurtosis and skewness of rCBV were statistically evaluated regarding prognosis performance[5]. However, a few other studies have demonstrated the inter subject variability in DSC parameters[39], which limit their applications in a clinical environment. Calculation of cerebral blood flow is also known to be affected by contrast agent leakage as a result of disruption of blood brain barrier (BBB) in malignant brain tumors. Further, a single statistic obtained from DCE-MRI may not be sufficient to capture the intra-tumor heterogeneity extant in GBM.

Radiomics, high-throughput extraction of quantitative imaging features from standard of care images, has recently emerged as a promising field to capture intra-tumoral heterogeneity on imaging. Radiomic features contain first-, second-, and higher-order statistics computed from descriptor map in a region of interest and could capture fine-grained texture characteristics. For instance, the gray-level co-occurrence matrix (GLCM) measures image texture properties between pixel pairs[40] and the gray-level run length matrix (GLRLM) reflects the distribution of a set of consecutive collinear voxels having

the same gray-level value[41]. Recently many routinely available imaging sequences in conjunction with radiomics approach have shown promising results in finding associations between quantitative imaging descriptors and clinical outcome in the context of Glioblastoma. For instance, Beig et al employed 30 radiomics features (i.e. Haralick, Laws energy, Gabor) from structural MRI scans (T1- Gd contrast, T2w, FLAIR) to capture molecular variations of tumor hypoxia, which is an important trait associated with survival. They identified a set of 10 radiomic features correlated with the extent of hypoxia, which were used to classify GBM patients into short-, mid- and long-term survival[6]. Similarly, Li et al proposed a fully automatic radiomic model for reproducibly evaluating prognosis of GBM patients using multiparametric signatures from T1w and T1 contrast MRI. They applied the least absolute shrinkage and selection operator (LASSO) Cox regression model on the training data set and eventually found out that 12 out of 36 signatures were correlated with overall survival[7]. Kim et al discovered that histogram parameters from apparent diffusion coefficients (ADC) are prognostic biomarkers to predict the survival of patients with treatment-naive GBM[8]. However, few studies have explored the role of radiomics in predicting survival in the context of perfusion imaging, where information on tumor heterogeneity is available in a dynamic fashion across different time phases during contrast administration.

A common methodology to quantify intensity spatial distribution using radiomics analysis is to acquire texture descriptors from grey-level co-occurrence matrix (GLCM), via quantifier functions like entropy or energy[9]. Recently Prasanna, P et al developed a new radiomic descriptor, Co-occurrence of Local Anisotropic Gradient Orientations

(CoLlAGe), to distinguish tumor confounders and molecular subtypes on MRI [10]. Previous studies have demonstrated that CoLIAGe could be utilized in a variety of cancer applications for tumor characterizations[13,14]. For instance, Shiradkar R et al found out that CoLIAGe from pretreatment biparametric MRI could predict biochemical recurrence of prostate cancer[13]. While highly promising, CoLIAGe has so far only been explored in the context of structural MRI. The rationale for using CoLIAGe features on DSC-perfusion imaging is that even though perfusion images of patients with different survival may look similar, they will differ in their local entropy patterns to some extent, in turn reflecting subtle local differences in tissue microarchitecture.

Previous study have shown that polynomial coefficients computed from breast DCE-MRI texture features could differentiate the benign tumors from those malignant ones[16]. Polynomial coefficients are related to the shape of curves in an affine invariant way[17] and it's likely that they would reflect difference of DyCoLIAGe expression across patients with varying survival characteristics. The rationale of using polynomial coefficients as predictors is that tumors from short-term survivors might have different contrast agent absorption over time compared to the tumors from patients with improved outcome and it is likely that this dynamic variation could be captured by the polynomial representations extracted from the DyCoLIAGe expression profile.

In this work, I present a new radiomic model, dynamic CoLIAGe (DyCoLIAGe), by extending CoLIAGe features on dynamic susceptibility contrast perfusion MRI. DyCoLIAGe will be applied on enhancing tumor region and infiltrative edema region to distinguish long-term from short-term survivors of GBM using pre-treatment DSC-MRI.

To further explore the difference of CoLIAGe profile changing over time between LTS and STS, I extracted polynomial coefficients from the DyCoLIAGe profile to quantify different powers of variation for each feature over different time phases.

I hypothesize that the DyCoLIAGe and the polynomial representations of the DyCoLIAGe profile from DSC-perfusion MRI could differentiate long-term from short-term survivors of GBM patients.

The rest of the paper is organized as follows. Section 2 describes the overall experimental design of this work (illustrated in Figure 1), including the data, registration and feature extraction, as well as the methodology for evaluating prognosis performance of both dynamic CoLIAGe descriptors and their corresponding polynomial representations. In Section 3, I present and discuss my experimental results followed by the concluding remarks in section 4.

2 Methodology

2.1 Data Description

Our retrospective study utilized dynamic susceptibility contrast (DSC) T2 perfusion MRI from 73 glioblastoma patients. The data set was obtained from three different cohorts on the publicly available The Cancer Imaging Archive (TCIA)[11]. Overall survival (OS) time was available for all patients and was defined as the time interval between the date of diagnosis and the date of death[29]. Patients who were still alive without the event of death on the last reported date were labeled as censored. Based on the median survival

time (t = 13.4 months) of all patients included in this study, I dichotomized the patients into long-term survivors (LTS) and short-term survivors (STS). These studies were split into training and testing set by including 2/3rd of the studies for training, while the remaining 1/3rd for testing. Each MRI dataset was acquired pre-operatively using a coil on a 3 Tesla MRI scanner, from a patient confirmed with grade IV glioblastoma based on the histology and who later underwent surgery followed by chemoradiotherapy.

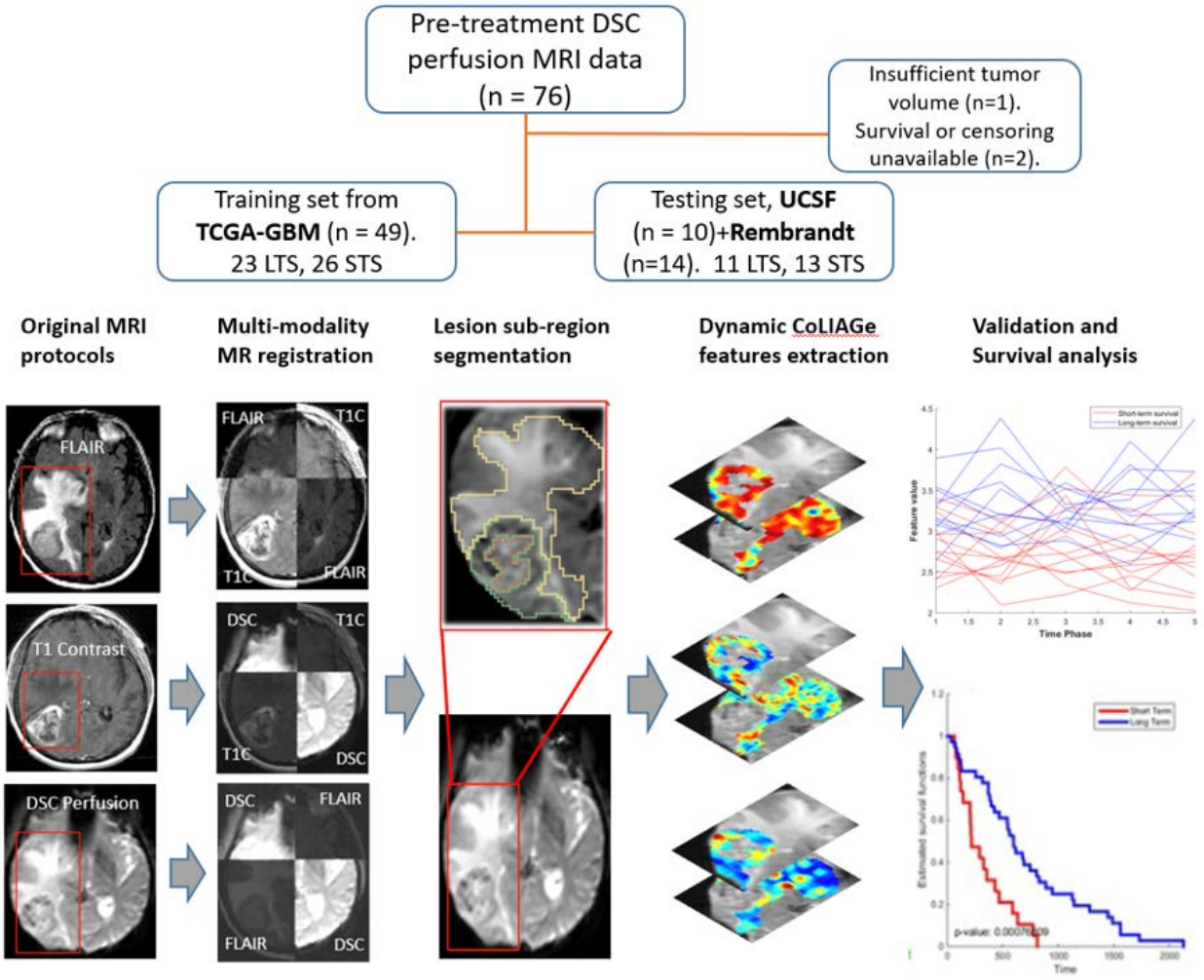

Figure 1 Data set overview and radiomic analysis workflow.

For each patient, the DSC perfusion MRI 2D slices from each individual time phase was acquired as a series of DICOM images, which were directly saved from the scanner (acquisition parameters summarized in Table 1). The raw DICOM data was restructured into MHA format using in-house developed software Dicomvert. Temporal resolution 2 seconds for all the cases with pixel dimensions of 128×128. Annotations were performed by an expert on the 2D slice with the biggest tumor size. The annotations were also confirmed by a senior radiologist.

Cohort		**Training set** ***TCGA-GBM***		***Testing set*** ***UCSF+Rembrandt***	
		Long-term survivors	***Short-term survivors***	***Long-term survivors***	***Short-term survivors***
Population (patients)		*23*	*26*	*11*	*13*
Mean OS (months)		*26.11*	*7.22*	*36*	*5.15*
Mean age (Years)		*53.6*	*55.4*	*54.3*	*56.75*
Gender	***Male***	*14*	*13*	*7*	*8*
	Female	*9*	*13*	*4*	*5*

Table 1 Demographics and clinical information of discovery and testing cohorts

2.2 Image Registration

Because the tumor boundaries are not as appreciable on perfusion scans, perfusion images were first registered to the corresponding T2w, FLAIR and T1 Gadolinium contrast enhanced MRI scans using 3D Slicer (4.8.0)[12]. An affine registration with 12 degrees of freedom encoding rotation, translation, sheer, and scale was applied and a nearest neighbor interpolation was used during registration.

2.3 Perfusion Time Span Standardization

Since my perfusion data were acquired from different institutions and different cohorts, the time in reference to contrast agent injection when the image series began varied between different patients. To address this issue, I standardized the time period across all dynamic scans before DyCoLIAGe feature extraction. Specifically, some studies were down-sampled so that all perfusion images from patients in training and testing set had the same time phase relative to peak contrast bolus time (signal intensity falls to minimum). Since temporal resolution is the same (2 sec) for all perfusion scans, they had the same number of time phases (T = 50) and all images are acquired for the same length of time during contrast manipulation.

2.4 Tumor Sub-Compartment Delineation

The 2-D slice with the largest visible tumor was annotated by an expert radiologist into 3 regions (1) edema,(2) tumor necrosis, and (3) enhancing tumor. Tumor necrosis on Gd-T1w is represented as areas of relatively hyper-intensed regions usually centrally located in the tumoral region. Hyper-intense FLAIR signals correlate with greater interstitial leakage and low cellular density, reflecting infiltrative edema outside the tumor.

2.5 Dynamic CoLIAGe Feature Extraction

CoLlAGe feature seeks to capture and exploit local anisotropic differences in voxel-level gradient orientations. It measures entropy disorder of co-occurrences of pixel/voxel-

level gradient orientations computed from the region of interest. The basic idea of CoLAIGe is to apply Haralick measures to the dominant gradient orientation within an n × n window, where n is the window size. Some measurements obtained via CoLIAGe quantify homogeneity of gradient orientations (e.g., CoLlAGe information measure of correlation), while some of them are reflective of gradient disorder (e.g., CoLlAGe entropy). Thirteen CoLIAGe descriptors are evaluated in this study. Four first-order statistics (median, standard deviation, skewness, and kurtosis) of each descriptor map were calculated for each tumor sub-region and phase included, which result in 52 statistical features on both edema and enhancing tumor. All feature extraction was performed in MATLAB, 2017b.

2.6 Computing Polynomial Kinetic Representations

Let $f_q^s(\mathrm{t})$ be the feature value at time t, where t ∈ $\{1, 2, \dots, \mathrm{T}\}$, q be the index for the CoLIAGe descriptor, q ∈ $\{1, 2, \dots, 13\}$, s indicates the statistic computed from the descriptor map and s ∈ $\{1,\ 2,\ 3,\ 4\}$. For each combination of q and s, I could get a CoLIAGe kinetic feature vector across the 50 time phases, $F_q^s = [f_q^s(1),\ f_q^s(2), \dots,\ f_q^s(\mathrm{T})]$. A third order polynomial is fitted to F_q^s to characterize its shape as

$$\widehat{F_q^s} = p_{q,3}^s\, t^3 + p_{q,2}^s\, t^2 + p_{q,1}^s\, t + p_{q,0}^s \qquad (1)$$

, where $[p_{q,3}^s,\ p_{q,2}^s,\ p_{q,1}^s,\ p_{q,0}^s\ ]$ are the model coefficients obtained by minimizing the root mean squared difference error between F_q^s and $\widehat{F_q^s}$. The reason for fitting the data into a 3rd order polynomial model is that the four coefficients in this model may be

sufficient to account for the variations of CoLIAGe expressions over time. I found out that when fitting our data into a higher polynomial model, most of the higher order coefficients were zero. Hence, I chose to fit our data to a 3rd order polynomial model.

2.7 Feature Selection and Model Building

I used the 4 coefficients that were computed for each feature using our 3rd polynomial fit, to train linear discriminant analysis and quadratic discriminant analysis classifiers for classification of patients as long-term or short-term survivors. Then I used a least absolute shrinkage and selection operator (LASSO) feature selection[19,20] in conjunction with a Cox Proportional Hazard model[21] to build a classification model for all the polynomial representations. The reason for using feature selection in this experiment is that each individual polynomial coefficient from a DyCoLIAGe profile will represent information for all time phases of that feature to some extent. For example, the first coefficient extracted from the first DyCoLIAGe feature represents magnitude of 3rd power variations of median DyCoLIAGe Entropy across all the time phases on edema region.

The LASSO method applies a shrinking (regularization) process where it penalizes the coefficients of the regression variables and shrinks some of them to zero. Depending on the regularization weight $\boldsymbol{\lambda}$, LASSO shrinks regression coefficients towards 0 to eliminate irrelevant features from the regression model[22]. I employed 5-fold cross validation to

find an optimal value of $\boldsymbol{\lambda}$. The goal of this process is to minimize the prediction error. LASSO has previously been extensively used for feature selection[23,24].

The combination of selected polynomial signatures and their coefficients are in the form of:

$$x_i^T \beta = x_1\beta_1 + x_2\beta_2 + \cdots + x_n\beta_n \quad (2)$$

, where x_n represent the selected polynomial coefficients and β_n are the model parameters. This combined signature could be regarded as a "risk score", representing the predicted relative hazard of death given the features from that patient[28].

The Cox proportional hazards model is similarly frequently used for survival prediction and survival outcome studies[25,26]. Based on the selected polynomial coefficients, a multivariate Cox regression analysis is performed on the training set to acquire the proportional hazard model parameters β_n.

2.8 Statistical and Survival Analysis

Hazard ratios (HR) were used to quantify individual feature effect on survival. Polynomial signatures yielding a HR between 0 and 1 are positively correlated with survival (i.e. lower signature values correlated with shorter survival). Then the median risk score from training set was set as a threshold to dichotomize patients into LTS and STS. Kaplan–Meier survival analysis[30] was used to examine the difference of overall survival between LTS and STS categorized by the classification output on both training

and testing set. The difference of OS was assessed by the log-rank test. P values were two-sided, and all values under 0.05 were considered to be statistically significant. The R package “glmnet” was used for LASSO Cox regression modeling[31,32].

3 Experimental evaluation

3.1 Experiment 1: Evaluation of DyCoLIAGe features in predicting overall survival

To evaluate prognostic performance of DyCoLIAGe profile, I first subsample the DyCoLIAGe values after every 10 phases of contrast injection on perfusion MRI. For each feature, corresponding feature values from time phase 5, 15, 25, 35, 45 were selected to reduce the redundancy of the input predictors. Since temporal resolution is 2 seconds for all the studies, time interval between two adjacent selected time phases is 20 seconds.

Then for each of the 52 CoLIAGe features on both edema and enhancing tumor, I fed the 5 feature values, from all different phases, separately into LDA and QDA classifiers. I performed 10 iterations of 3 fold-cross-validation in the training set to identify features with optimal classification performance between the two survival groups (long-term versus short-term survivors). I chose these two classifiers owing to the fact that they have no hyper-parameters to tune and are able to learn both linear and quadratic boundaries. Area under receiver operating characteristic curve (AUC) is obtained for

each iteration, for every feature. Features with mean AUC above 0.6 across the 10 iterations in the training set were selected as top features and their classification performance were separately evaluated in the test set.

3.2 Experiment 2: Evaluation of polynomial signatures from DyCoLIAGe in predicting overall survival

To evaluate prognostic performance of polynomial signatures from DyCoLIAGe features, I computed the four coefficients for the 3rd order polynomial model for each of the 52 DyCoLIAGe features. Similar to the method in Experiment 1, I first evaluated coefficients from each DyCoLIAGe feature in distinguishing the two survival groups using LDA and QDA classifiers. AUC and accuracy were reported for top features in both training and hold out testing set.

To further do a survival analysis, I fed all the coefficients from all features across the two tumor sub-compartments from the training set, into a LASSO model. To find an optimal model parameter λ, 5-fold cross validation with minimum criteria was employed, where the final value of λ provided minimum cross validation error. The retained polynomial representations with nonzero coefficients were used for multivariate Cox regression model fitting and combined into a risk score as illustrated in Equation 2. A relative high-risk score for a specific patient in testing set is predicted to have high level of hazard, thus may have a poor survival based on the selected signatures and model parameters

learned from the training set. Based on the median risk score obtained on the hold-out test set, I classified each patient as a long-term or short-term survivor.

4 Results and Discussion

4.1 Experiment 1: Evaluation of DyCoLIAGe features in predicting survival

Table 2 summarizes top DyCoLIAGe features and top polynomial representations computed from DyCoLIAGe profile in descending order of AUC on the testing set (n=24). The most significant feature belongs to variance of sum of variance on enhancing tumor region. When applied to a QDA classifier, a mean AUC of 0.71 was obtained across 10 iterations of cross validation in the training set and an AUC of 0.78 on the retrospective validation cohort. Figure 2 shows the plots for this feature over time on both the training (a) and the testing (b) cohort. Figure 3 (a) illustrates two sum of variance feature curves for one long-term survivors (blue, t=55.3 months) and one short-term survivors (red, t=4.6 months) over five-time phases. Figure 3 (b) provides enhancing tumor region for these two patients, with the same color of the curves and Figure 3 (c) is a visualization of the feature distribution over time phases.

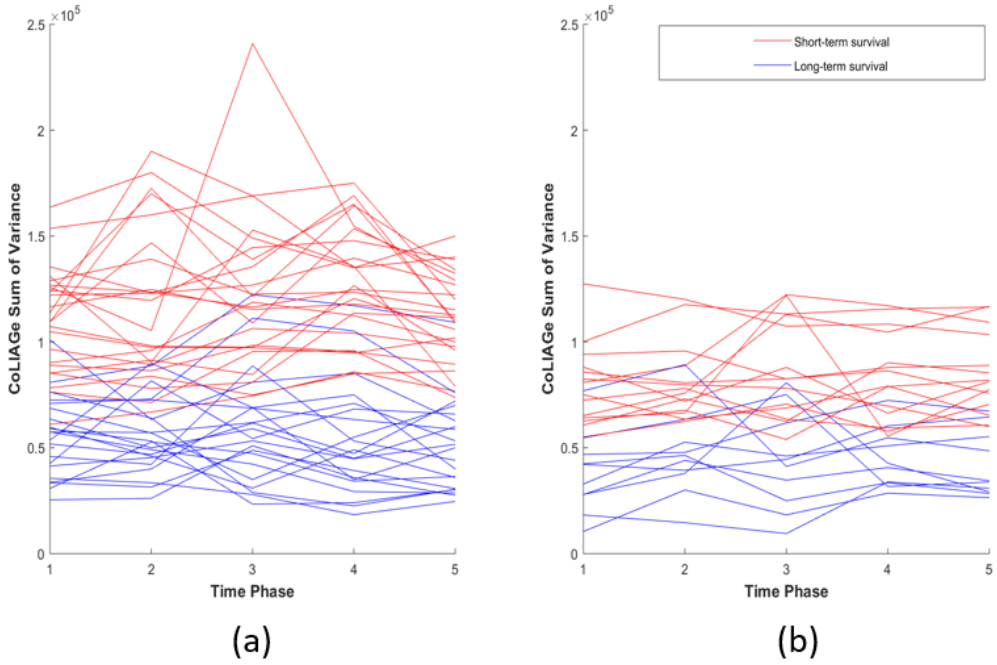

Figure 2 Dynamic variance of CoLIAGe sum of variance for long-term (blue) and short-term (red) survivors on training (a) and testing (b) cohorts.

Among the 4 optimal features, three features, kurtosis of correlation (AUC=0.72), kurtosis of information-2 (AUC=0.69) and median of correlation (AUC=0.65) were obtained from the edema region. This result is consistent with the previous finding[33], in which radiomic features from edema were reported to be predictive of overall survival in GBM patients.

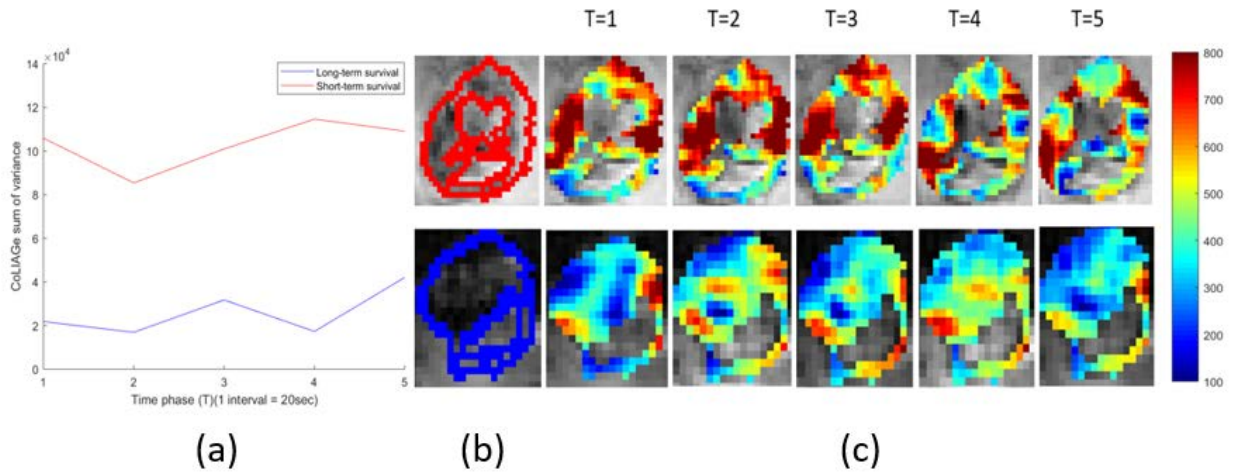

Figure 3 (a) Dynamic variance of CoLIAGe sum of variance for long-term (survival = 55.3 months, blue) and short-term (survival = 4.6 months, red) survivor. (b) Enhancing tumor region. (c) Feature map over time.

4.2 Experiment 2: Evaluation of polynomial signatures from DyCoLIAGe in predicting overall survival

The best polynomial representations were from median of CoLIAGe information-2 obtained from the edema region. Combined with a QDA classifier, it yielded an AUC of 0.62 on the training set and 0.71 on the test set. Interestingly, only kurtosis of correlation was picked up to be associated with survival in both Experiments 1 and 2.

#	Tumor Sub-region	Descriptor	Statistic	Classifier used	AUC on training	AUC on testing
Experiment using DyCoLIAGe features to predict survival						
1	Enhancing tumor	Sum of Variance	Variance	QDA	0.71	0.78
2	Edema	Correlation	Kurtosis	LDA	0.63	0.72
3	Edema	Information-2	Kurtosis	LDA	0.74	0.69
4	Enhancing tumor	Sum of Variance	Variance	LDA	0.61	0.68
5	Edema	Correlation	Median	QDA	0.64	0.65
Experiment using polynomial representations from DyCoLIAGe to predict survival						
1	Edema	Information-2	Median	QDA	0.62	0.71
2	Edema	Energy	Median	QDA	0.64	0.63
3	Enhancing tumor	Correlation	Kurtosis	LDA	0.63	0.63
4	Enhancing tumor	Entropy	Skewness	QDA	0.61	0.58

Table 2 Predictive DyCoLIAGe features and polynomial coefficients from DyCoLIAGe on edema and enhancing tumor and corresponding AUC on training and testing data set

When I combined all the polynomial representations from both edema and enhancing tumor and fed them into a LASSO feature selection model, a total of 6 polynomial coefficients were identified with non-zero coefficients. Table 3 lists hazard ratio and statistical significance when fitting these 6 polynomial coefficients into the Cox model.

Polynomial Coefficients	95% confidence interval for Hazard Ratio in final Cox model	p-value
1st power of Skewness of diff-av on enhancing tumor	0.7-0.9	0.000837
2nd power of kurtosis of	2.1-2.77	0.003

information-2 on edema		
2nd power of kurtosis of entropy on enhancing tumor	0.69-0.98	0.004
1st power of kurtosis of idm on edema	0.77-0.94	0.005
2nd power of median of energy on edema	0.91-0.98	0.03
2nd power of median of sum-av on enhancing tumor	1.08 8.47	0.048

Table 3Polynomial coefficients in the final Cox model.

Figure 4 shows the KM curves on the training (left) and test (right) set obtained using selected polynomial signatures from edema and enhancing tumor. The concordance index (CI)[34,35] were found to be 0.85 and 0.83, respectively.

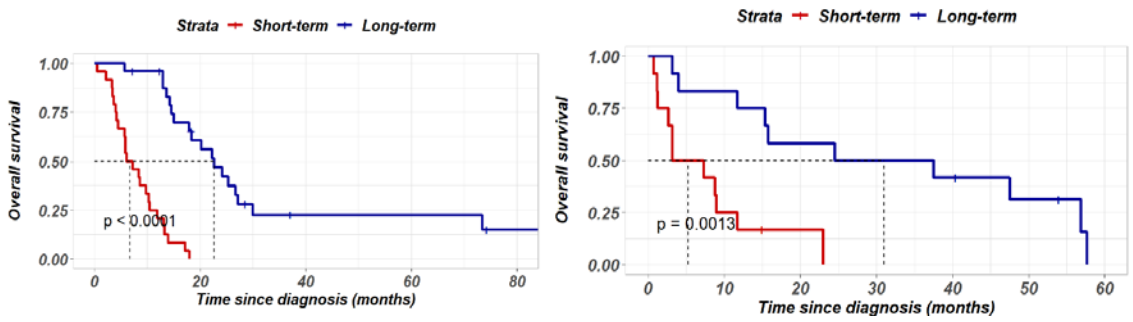

Figure 4 Kaplan-Meier curves generated using the 6 polynomial coefficients to distinguish long-term and short-term survivors in training (left) and testing (right) data set.

4.3 Discussion

In this study, I presented a noninvasive radiomic approach to predict overall survival in Glioblastoma based on DyCoLIAGe extracted from pre-treatment DSC perfusion MRI at multiple time phases. Quantitative imaging features from multiple image modalities have shown to have prognostic value for patient outcome prediction[6,36]. A few studies have investigated the role of dynamic susceptibility-weighted contrast (DSC) perfusion

MRI in glioma diagnosis[37], outcome prediction[5] and treatment evaluation[38]. Parameters such as maximum relative cerebral blood volume (rCBVmax)[3] and maximum relative cerebral blood flow (rCBFmax)[4] have been explored previously in predicting overall survival. Histogram analysis of these parameters has also been conducted by Romano, A. et al to verify their prognostic values[5]. However, it's likely that the intra-tumor heterogeneity of GBM and the variation of interaction between tumor and the contrast agent over time may not be fully captured by utilizing rCBV or rCBF alone. My method computes 4 statistics from across 13 descriptors from CoLIAGe feature family to stratify the patients into long-term and short-term survivors. All of these features are reflections of local intensity gradient orientation. For example, correlation is a measure of association in gradient orientation between the pixels in the pre-specified region. The more similar the gradient orientation, the higher the correlation. My results show that multiple DyCoLIAGe features have optimal prognostic value on both training and test cohorts. Among these features, sum of variance from enhancing tumor turned out to be the most significant feature. A higher variation of sum of variance on enhancing tumor indicated poor survival, compared to those with improved outcome.

I also applied polynomial coefficients from the DyCoLIAGe feature curve to perform classification between the two survival groups. I believe that the changes in interaction between tumor and contrast agent susceptibility over time may be different for long-term and short-term survivors of GBM. Shape of dynamic DyCoLIAGe feature curves may be able to capture this difference and may be manifested by the combination of various polynomial coefficients. My results showed that 6 polynomial coefficients which

were significantly correlated with overall survival were selected using LASSO feature selection. The final Cox model with these polynomial coefficients yielded optimal separation between the long-term and short-term survival groups.

5 Concluding remarks

Below are the key take aways for my study:

1. Dynamically extracted gradient-based radiomic descriptors from edema and enhancing tumor on pre-treatment DSC perfusion MRI may be able to predict survival. Results show that higher variations of sum of variance on both edema and enhancing tumor from perfusion imaging indicates poor survival.
2. Polynomial representations computed from dynamic feature curve provide information on the shape of the curves over time and this information may be associated with patient survival outcome. A combined polynomial signature yielded improved prognostic value compared with individual predictors.

Despite my effort in exploring the prognostic value of different radiomic features, I do acknowledge a few limitations. Though I standardized all perfusion image scans into the same time period, I did not normalize the feature values across all patients. My study was also limited by a relatively small number of patients. Because of this, a large independent validation of the radiomic features could not be performed.

Other aspects I could include in the future may be to improve prognostic performance by integrating CoLIAGe features from perfusion MRI with other structural multi-parametric MRI scans. I could also perform studies to see if combining the DyCoLIAGe features with the rCBV and rCBF parameters could improve prognostic ability of our model.

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