



Overall Survival Time Prediction of Glioblastoma on Preoperative MRI Using Lesion Network Mapping

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Abstract. Glioblastoma (GBM) is the most aggressive malignant brain tumor. Its poor survival rate highlights the pressing need to adopt easily accessible, non-invasive neuroimaging techniques to preoperatively predict GBM survival, which can benefit treatment planning and patient care. MRI and MRI-based radiomics, although effective for survival prediction, do not consider brain's functional alternations caused by tumors, which are clinically significant for guiding therapeutic strategies aimed at inhibiting tumor-brain communication. In this paper, we propose an augmented lesion network mapping (A-LNM) based survival prediction framework, where a novel neuroimaging feature family, called functional lesion network (FLN) maps generated by the A-LNM, is achieved from patients' structural MRI, and thus are more readily available than functional connections measured with functional MRI of patients. Specifically, for each patient, the A-LNM first estimates functional disconnection (FDC) maps by embedding the lesion (the whole tumor) into an atlas of functional connections in a large cohort of healthy subjects, and many FLN maps are then obtained by averaging subsets of the FDC maps such that we can artificially boost data volume (i.e., FLN maps), which helps to mitigate over-fitting and improve survival prediction performance when learning a deep neural network from a small sized dataset. The augmented FLN maps are finally fed to a 3D ResNet-based backbone followed by the average pooling operation and fully-connected layers for GBM survival prediction. Experimental results on the BraTS 2020 training dataset demonstrate the effectiveness of our proposed framework with the A-LNM derived FLN maps for GBM survival classification. Moreover, we identify the survival-relevant brain regions that can be traced back with biological interpretability.

Keywords: Brain tumor · functional connections · lesion network mapping · survival prediction

1 Introduction

Glioblastomas (GBMs, known as grade IV gliomas) are the most common primary malignant brain tumors with high spatial heterogeneity and varying degrees of aggressiveness [22]. Patients with GBM generally have a very poor survival rate; the median overall survival time is about 14 months [17]; and the overall survival time is affected by many factors, including patient characteristics (e.g., age and physical status), tissue histopathology (e.g., cellular density and nuclear atypia), and molecular pathology (e.g., mutations and gene expression levels) [1, 14, 15]. Although these factors, particularly molecular information, have usually proved to be strong predictors of survival in GBM, there remain substantial challenges and unmet clinical needs to exploit easily accessible, non-invasive neuroimaging data acquired preoperatively to predict overall survival time of GBM patients, which can benefit treatment planning.

To do so, magnetic resonance imaging (MRI) and its derived radiomics have been widely used to study GBM preoperative prognosis over the last few decades. For example, Anand et al. [2] first applied a forest of trees to assign an importance value to each of the 1022 radiomic features extracted from T1 MRI, and then the 32 most important features were fed to the random forest regressor for predicting overall survival time of a GBM patient. Based on patches from multi-modal MRI images, Nie et al. [19] trained a 3D convolutional neural network (CNN) to learn the high-level semantic features, which were eventually input to a support vector machine (SVM) for classifying long- and short-term GBM survivors. In addition, an integrated model by fusing radiomics features, MRI-based CNN features, and clinical features, was presented for GBM survival group classification, resulting in better performance than using any single type of features [12].

Although both MRI and its derived radiomics features have been demonstrated to have predictive power for survival analysis in the aforementioned literature, they do not account for brain's functional alternations caused by tumors, which are clinically significant as biologically-interpretable biomarkers of recovery and therapy. These alternations can be reflected by changes in resting-state functional MRI (fMRI)-derived functional connectivities/connections (FCs) between the blood oxygenation level-dependence (BOLD) time series of paired brain regions. Therefore, the use of FCs to predict overall survival time for GBM has recently attracted increasing attention [7, 16, 24], and more importantly, survival-related FC patterns or brain regions were found to guide therapeutic solutions aimed at inhibiting tumor-brain communication.

Nevertheless, current FC-based survival prediction still suffers from two main deficiencies when applied to GBM prognosis. First, due to mass effect and physical infiltration of GBM in the brain, FCs estimated directly from GBM patients' resting-state fMRI might be inaccurate, especially when the tumors are near or in the regions of interest. Second, resting-state fMRI data are not routinely collected for GBM clinical practices, which restricts the size of annotated datasets such that it is infeasible to train a reliable prediction model based on deep learning for survival prediction. In order to circumvent these issues, in this paper we introduce a novel neuroimaging feature family, namely functional lesion network

(FLN) maps that are generated by our augmented lesion network mapping (A-LNM), for overall survival time prediction of GBM patients. Our A-LNM is motivated by lesion network mapping (LNM) [8] which can localize neurological deficits to functional brain networks and identify regions relate to a clinical syndrome. By embedding the lesion into a normative functional connectome and computing functional connectivity between the lesion and the rest of the brain using fMRI of all healthy subjects in the normative cohort, LNM has been successfully employed to the identification of the brain network underlying particular symptoms or behavioral deficits in stroke [4, 13].

The details of our workflow are described as follows.

- 1) We first manually segment the whole tumor (regarded as lesion in this paper) on structural MRI for all GBM patients, and the resulting lesion masks are mapped onto a reference brain template, e.g., the MNI152 2mm³ template.
- 2) The proposed A-LNM is next used to generate FLN maps for each GBM patient by using resting-state fMRI from a large cohort of healthy subjects. Specifically, for each patient, we correlate the mean BOLD time series of all voxels within the lesion with the BOLD time series of every voxel in the whole brain for all N subjects in the normative cohort, producing N functional disconnection (FDC) maps of voxel-wise correlation values (transformed to z-scores). These resulting N FDC maps are partitioned into M disjoint subsets of equal size, and M FLN maps are separately obtained by averaging the FDC maps in each of the M subsets. Similar to data augmentation schemes, we can artificially boost data volume (i.e., FLN maps) up to M times through producing M FLN maps for each patient in the A-LNM, which helps to mitigate the risk of over-fitting and improve the performance of overall survival time prediction when learning a deep neural network from a small sized dataset. For this reason, we propose the name “augmented LNM (A-LNM)”, compared to the traditional LNM where only one FLN map is generated per patient by averaging all the N FDC maps.
- 3) Finally, these augmented FLN maps are fed to a 3D ResNet-based backbone network followed by the average pooling operation and fully-connected layers for GBM survival prediction.

To our knowledge, this paper is the first to demonstrate a successful extension of LNM for survival prediction in GBM. To evaluate the predictive power of the FLN maps generated by our A-LNM, we conduct extensive experiments on 235 GBM patients in the training dataset of BraTS 2020 [18] to classify the patients into three overall survival time groups viz. long, mid, and short. Experimental results show that our A-LNM based survival prediction framework outperforms previous state-of-the-art methods. In addition, an explainable analysis driven by the Gradient-weighted Class Activation Mapping (Grad-CAM) [10] for survival-related brain regions is fulfilled.

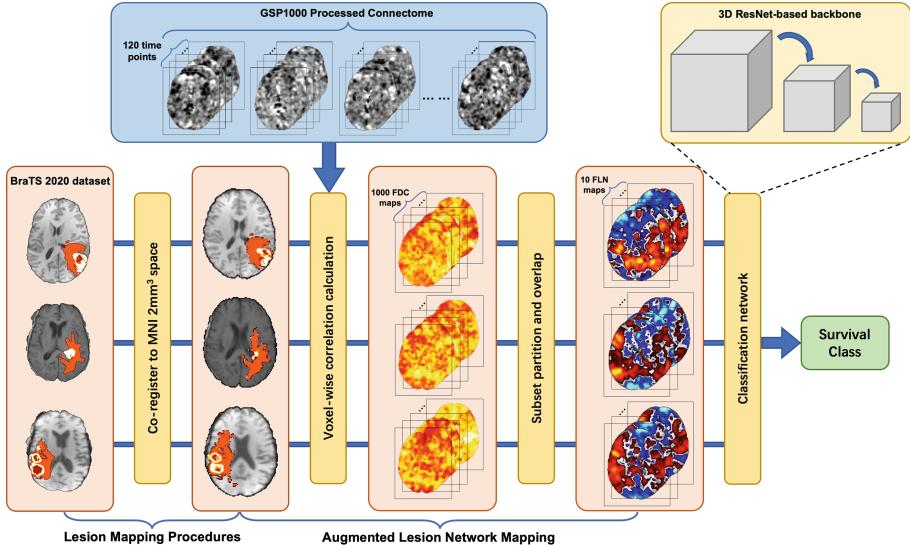


Fig. 1. The proposed framework for GBM survival prediction.

2 Materials and Methods

2.1 Materials

GSP1000 Processed Connectome. It publicly released preprocessed resting-state fMRI data of 1000 healthy right-handed subjects with an average age 21.5 ± 2.9 years and approximately equal numbers of males and females from the Brain Genomics Superstruct Project (GSP) [5], where the concrete image acquisition parameters and preprocessing procedures can be found as well. Specifically, a slightly modified version of Yeo's Computational Brain Imaging Group (CBIG) fMRI preprocessing pipeline (<https://github.com/bchcohenlab/CBIG>) was employed to obtain either one or two preprocessed resting-state fMRI runs of each subject that had 120 time points per run and were spatially normalized into the MNI152 template with 2mm^3 voxel size. We downloaded and used the first-run preprocessed resting-state fMRI of each subject for the following analysis.

BraTS 2020. It provided an open-access pre-operative imaging training dataset to segment brain tumors of glioblastoma (GBM, belonging to high grade glioma) and low grade glioma (LGG) patients, as well as to predict overall survival time of GBM patients [18]. This training dataset contained 133 LGG and 236 GBM patients, and each patient had four MRI modalities, including T1, post-contrast T1-weighted, T2-weighted, and T2 Fluid Attenuated Inversion Recovery. Manual expert segmentation delineated three tumor sub-regions, i.e., the GD-enhancing tumor, the peritumoral edema, and the necrotic and non-enhancing tumor core.

The union of all the three tumor sub-regions was considered as the whole tumor, which is regarded as the lesion in this paper.

2.2 Methods

In this paper, we propose to investigate the feasibility of the novel neuroimaging features, i.e., FLN maps, for overall survival time prediction of GBM patients in the training dataset of the BraTS 2020, in which one patient alive was excluded, and the remaining 235 patients consisted of 89 short-term survivors (less than 10 months), 59 mid-term survivors (between 10 and 15 months), and 87 long-term survivors (more than 15 months). To this end, our framework for the three-class survival classification is shown in Fig. 1, and the details are described as follows.

Lesion Mapping Procedures. As stated above, the whole tumor is referred to as a lesion for each GBM patient. From the manual expert segmentation labels of lesions in the 235 GBM patients of the BraTS 2020, we co-register the lesion masks to the MNI152 2mm³ template by employing a Symmetric Normalization algorithm in ANTsPy [3].

Augmented Lesion Network Mapping (A-LNM). After lesion mapping, we introduce a modified LNM (called augmented LNM (A-LNM) in this paper) to generate FLN maps for each GBM patient by using resting-state fMRI of all 1000 GSP healthy subjects, as described below. *i)* For each patient, the lesion is viewed as a seed region to calculate FDC in the healthy subjects with resting-state fMRI. Specifically, to compute FDC, the mean BOLD time series of voxels within each lesion is correlated with the BOLD time series of every voxel in the whole brain for all the 1000 healthy subjects, yielding 1000 FDC maps of voxel-wise correlation values (transformed to z-scores), where an FDC map is actually a three-dimensional voxel-wise matrix of size 91 × 109 × 91 (spatial resolution: 2mm³ voxel size). *ii)* Different from the commonly used LNM where the resulting 1000 FDC maps are thresholded or averaged to obtain a single FLN map for each patient, the A-LNM generates many FLN maps for each patient in a manner that partitions all the 1000 FDC maps into disjoint subsets of equal size and averages each subset to produce one FLN map. One can clearly see that similar to data augmentation schemes, we artificially boost the number of training samples (i.e., FLN maps) by our A-LNM, which helps to mitigate the risk of over-fitting and improve the performance of overall survival time prediction when learning a deep neural network from such a small sized training set used in this paper. Note that in Sect. 3 of this paper, according to experimental results, we divided the 1000 FDC maps into 100 subsets, and randomly chose 10 out of the resulting 100 FLN maps for each patient as input to the downstream prediction model.

Deep Neural Network for Overall Survival Time Prediction. By taking the obtained FLN maps as input, we apply a 3D ResNet-based backbone network transferred from the encoder of MedicalNet [6] to extract CNN features from each FLN map. The features are then combined using the average pooling operation and fed to a fully-connected layer with kernel size (1, 1, 1) to classify each GBM patient into one of the three overall survival time groups (i.e., short-term survival, mid-term survival, and long-term survival).

3 Experiments and Results

3.1 Experimental Settings

Implementation Details. Our proposed method was implemented in PyTorch 1.13.1 on NVIDIA A100 Tensor Core GPUs. The loss function was the standard cross-entropy loss. The Adam optimizer with the weight decay of 10^{-5} was adopted. Three 3D ResNet-based backbones with different numbers of layers (10, 50, and 101) were performed, where the initial learning rates were set as 10^{-4} , 10^{-4} , and 10^{-5} , respectively, and would decrease by a factor of 5 if the classification performance is not improved within 5 epochs. The number of epochs for training was 50, and the batch size was fixed as 64.

Performance Evaluation. We evaluated the classification performance of our proposed method using 235 GBM patients in the BraTS 2020 training dataset, because only these 235 patients had both overall survival time and manual expert segmentation labels of lesions. In all experiments, we conducted five-fold cross-validation ten times in order to reduce the effect of sampling bias. Moreover, the A-LNM was performed ten times randomly to avoid particular data distribution and obtain more reliable results. The classification results were reported in terms of accuracy, macro precision (macro-P), macro recall (macro-R), and macro F1 score (macro-F1), respectively.

3.2 Comparison Studies

Quantitative Comparison of Different Prediction Models. As this paper is the first application of FLN maps in the overall survival time prediction for GBM, comparison among the classification performance of different models using the same type of features, i.e., the A-LNM or the LNM derived FLN maps, is demanded for model selection. To validate the effectiveness of the 3D ResNet-based backbones for GBM survival prediction, we made quantitative comparison of a ridge classifier (RC) with PCA [23], a support vector classifier (SVC) with PCA, a logistic regression (LR) with PCA, and three 3D ResNet-based backbones with different numbers of layers (10, 50, and 101). As presented in Table 1, all the 3D ResNet-based backbones outperformed the other three machine learning-based models. In addition, all the 3D ResNet-based backbones achieved better classification results by using the A-LNM derived FLN maps than the LNM derived FLN maps, which implies that the A-LNM derived FLN maps have stronger predictive power than the LNM derived FLN maps.

Table 1. Quantitative comparison of different prediction models on the BraTS 2020 training dataset. (mean \pm sd)

Feature	Model	Accuracy	macro-P	macro-R	macro-F1
FLN maps (LNM)	RC with PCA	0.475 \pm 0.030	0.320 \pm 0.035	0.426 \pm 0.014	0.365 \pm 0.024
	LR with PCA	0.487 \pm 0.029	0.428 \pm 0.047	0.441 \pm 0.034	0.434 \pm 0.039
	SVC with PCA	0.483 \pm 0.039	0.328 \pm 0.070	0.438 \pm 0.050	0.375 \pm 0.041
	3D ResNet-10	0.553 \pm 0.065	0.460 \pm 0.039	0.548 \pm 0.042	0.500 \pm 0.043
	3D ResNet-50	0.511 \pm 0.046	0.359 \pm 0.037	0.455 \pm 0.034	0.401 \pm 0.041
	3D ResNet-101	0.468 \pm 0.076	0.319 \pm 0.054	0.437 \pm 0.040	0.369 \pm 0.046
FLN maps (A-LNM)	3D ResNet-10	0.658 \pm 0.047	0.604 \pm 0.032	0.639 \pm 0.037	0.621 \pm 0.032
	3D ResNet-50	0.632 \pm 0.048	0.622 \pm 0.054	0.623 \pm 0.038	0.622 \pm 0.036
	3D ResNet-101	0.532 \pm 0.051	0.379 \pm 0.125	0.464 \pm 0.037	0.417 \pm 0.044

Quantitative Comparison of Different Types of Features. Subsequently, we compared the predictive power of FLN maps and the other four widely used types of features, i.e., clinical features with an LR [27], biophysics features with an SVC [9], radiomics features with a gradient boosting classifier (GBC) [21], and MRI-based features with a 3D CNN model [9]. These competing models were executed following the instructions in their respective papers to achieve the best performance. Quantitative results of different types of features are displayed in Table 2. One can see that FLN maps showed the strongest predictive power on all the four metrics. Specifically, the 3D ResNet-10 backbone with the A-LNM derived FLN maps improved the classification performance by 10.5% to 18.5% in terms of accuracy, which again demonstrates the superiority of the A-LNM derived FLN maps for GBM survival prediction.

Table 2. Quantitative comparison of different types of features on the BraTS 2020 training dataset. (mean \pm sd; \dagger : p-value $<$ 0.05)

Feature & Model	Accuracy	macro-P	macro-R	macro-F1
clinical features + LR [27]	0.473 \pm 0.080 \dagger	0.319 \pm 0.053 \dagger	0.424 \pm 0.034 \dagger	0.364 \pm 0.042 \dagger
biophysics features + SVC [9]	0.498 \pm 0.064 \dagger	0.338 \pm 0.038 \dagger	0.446 \pm 0.053 \dagger	0.385 \pm 0.044 \dagger
radiomics features + GBC [21]	0.549 \pm 0.050 \dagger	0.533 \pm 0.036 \dagger	0.522 \pm 0.027 \dagger	0.527 \pm 0.031 \dagger
MRI images + 3D DenseNet-121 [9]	0.545 \pm 0.047 \dagger	0.525 \pm 0.031 \dagger	0.513 \pm 0.035 \dagger	0.519 \pm 0.032 \dagger
FLN maps (LNM) + 3D ResNet-10	0.553 \pm 0.065 \dagger	0.460 \pm 0.039 \dagger	0.548 \pm 0.042 \dagger	0.500 \pm 0.043 \dagger
FLN maps (A-LNM) + 3D ResNet-10	0.658 \pm 0.047	0.604 \pm 0.032	0.639 \pm 0.037	0.621 \pm 0.032

3.3 Brain Regions in Relation to GBM Survival

To identify the most discriminative brain regions associated with overall survival time in GBM, we estimated the relative contribution of each voxel to the classification performance in our proposed method by using the Grad-CAM [10]. To

obtain steady results, as shown in Fig. 2(A), the voxels with top 5% weights in the class activation maps (CAMs) of all candidate models were overlapped by class, and the position covered by more than half of the models is displayed. The CAMs of three classes of survivors overlapped in Fig. 2(B) where both coincident and non-coincident areas exist. The association of an increased degree of invasion within the frontal lobe with decreased survival time can be observed, which is in concordance with a previous study [20]. Patients whose frontal lobe is affected by tumors showed more executive dysfunction, apathy, and disinhibition [11]. On the dominant left hemisphere, the CAMs of long-term survivors and mid-term survivors overlapped at the superior temporal gyrus and Wernicke's area which are involved in the sensation of sound and language comprehension respectively, and have been associated with decreased survival in patients with high-grade glioma [26]. In addition, the CAM of mid-term survivors covered more areas of the middle and inferior temporal gyri which were considered as one of the higher level ventral streams of visual processing linked to facial recognition [25].

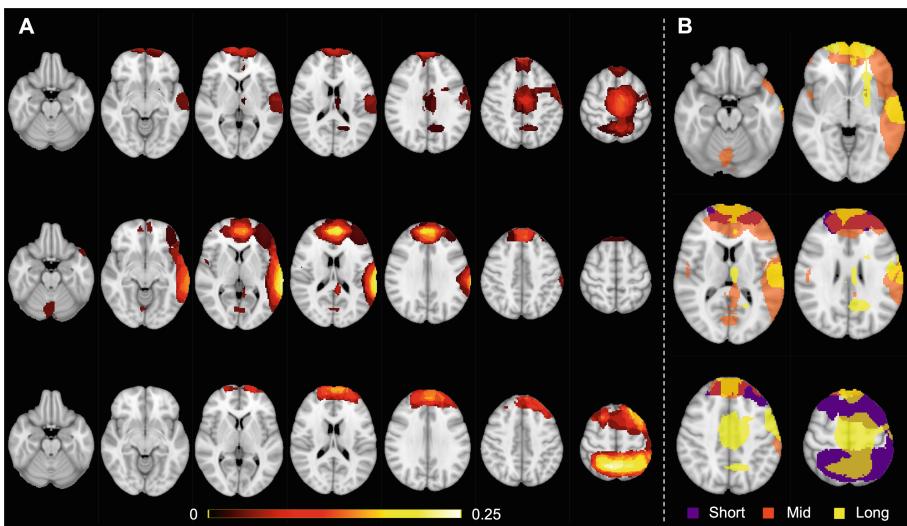


Fig. 2. (A) The processed class activation maps of long-term, mid-term, and short-term survivors from the top down. The color scale indicates the average weights of class features. (B) The overlapped class activation map of long-term, mid-term, and short-term survivors where the purple color, orange color, and yellow color represent the map of short-term, mid-term, and long-term survivors respectively. (Color figure online)

4 Conclusion

In this paper, we introduce a novel neuroimaging feature family, called A-LNM derived FLN maps, for overall survival time prediction of GBM patients. A-LNM was presented to generate plenty of FLN maps for each GBM patient by partitioning the FDC maps obtained from resting-state fMRI of 1000 GSP healthy subjects into disjoint subsets of equal size and averaging each subset. We applied a 3D ResNet-based backbone network to extract features from the generated FLN maps and classify GBM patients into three overall survival time groups. Experimental results on the BraTS 2020 training dataset validated the effectiveness of the A-LNM derived FLN maps for GBM survival prediction. Moreover, a visualization analysis implemented by the Grad-CAM revealed the brain regions associated with GBM survival. In future work, we will try to fuse the FLN maps and MRI-based radiomics features to study their combined predictive power for GBM survival analysis.

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