Leveraging Unlabeled Data for Glioma Molecular Subtype and Survival Prediction

Nicholas Nuechterlein[1], Beibin Li[1], Mehmet Saygin Seyfioğlu[2], Patrick J. Cimino[3,4], Linda Shapiro[1,2]

[1]Paul G. Allen School of Computer Science & Engineering, University of Washington, Seattle, WA, USA, [2]Department of Electrical & Computer Engineering, University of Washington, Seattle, WA, USA, [3]Division of Human Biology, Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [4]Department of Pathology, Division of Neuropathology, University of Washington, Seattle, WA, USA

ABSTRACT

Background: The 2016 World Health Organization (WHO) criteria organize diffuse gliomas into broad, survival-stratifying molecular subtypes based on the mutation status of the genes IDH1 and IDH2 and the co-deletion status of whole chromosome arms 1p and 19q. The potential for unlabeled magnetic resonance (MR) imaging data to aid the prediction of glioma molecular subtype and survival remains unknown. Multi-task learning (MTL) is a strategy capable of recruiting unlabeled MR data for such prediction tasks through the joint learning of an axillary tumor segmentation task.

Methods: We propose a novel application of MTL that jointly learns an auxiliary tumor segmentation task with glioma molecular subtype that can learn from patients with and without genomic data. We analyze multi-parametric MR data from 542 patients in the combined training, validation, and testing sets of the 2018 Multimodal Brain Tumor Segmentation (BraTS) Challenge and somatic copy number alteration (SCNA) data from 1090 patients in The Cancer Genome Atlas' (TCGA) lower-grade glioma and glioblastoma projects.

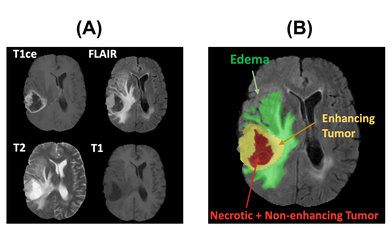
Results: Our MTL model trained with unlabeled MR data accurately predicts IDH1/2 mutations (AUC = 0.89) and 1p/19q co-deletions (AUC = 0.87) and outperforms comparable 3D convolutional neural networks (CNNs) trained on labeled MR imaging data alone. Training with SCNA data dramatically boosts subtype performance (AUC > 0.98) and raises the survival C-index score of survival models trained on embeddings generated by IDH1/2 prediction models from 0.719 to 0.735.

BACKGROUND: MR DATA AND LABEL DISTRIBUTION

Figure 1. Datasets. The partially overlapping BraTS MR imaging and TCGA glioma SCNA datasets have a mixture of molecular subtype (IDH1/2 mutation & 1p/19q co-deletion), overall survival, and tumor segmentation labels.

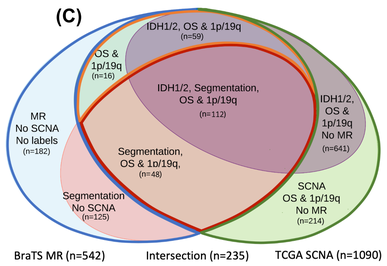
A) 2D slices of four volumetric MR modalities describing an IDH1/2-wildtype patient's tumor. Tumor ring enhancement is visible on the T1ce modality.

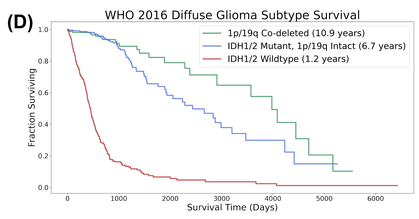
B) Ground truth segmentation mask with segmentation classes labeled.



C) Distribution of labels in the merged BraTS and TCGA glioma SCNA datasets. *Red boundary*: labeled training set; *gold boundary*: validation set; *blue boundary*: unlabeled MR data; *green boundary*: samples with SCNA data but without MR data.

D) Glioma molecular subtypes defined by IDH1/2 mutations and 1p/19q co-deletions stratify patient survival.





MODEL ARCHITECTURE AND RESULTS

Figure 2. (A) Multi-task learning model. We add a classification branch to the output of the encoder of a U-Net-style segmentation network. PCA-reduced SCNA data is passed though fully connected layers, concatenated with the average-pooled encoder output, and fed into a classifier to predict molecular subtype class. Our model accepts full brain multi-model MR volumes as well as cropped tumor volumes (shown here). We train models on 4-channel MR data input and 1-channel, single-modality input.

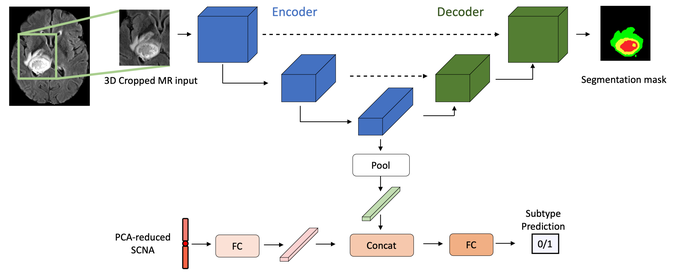


Table 1 shows IDH1/2 mutation, 1p/19q co-deletion, and survival prediction results for models trained on an array of different MR inputs including cropped and single MR sequence volumes. Our models give the most improvement across tasks when trained on whole brain, all modality input; they give the most improvement to 1p/19q co-deletion and survival prediction across all inputs.

Input Modalities	IDH1/2 Mutation (ROC-AUC)		1p/19q Co-deletion (ROC-AUC)		Overall Survival (C-index)	
	CNN	MTL (MR)	CNN	MTL (MR)	MTL (MR)	MTL (MR+SCNA)
All (Whole Brain)	0.669	**0.846**	0.605	**0.813**	0.587	**0.723**
All (Cropped)	0.872	**0.894**	0.744	**0.871**	0.697	**0.732**
T1ce (Cropped)	**0.893**	0.884	0.772	**0.819**	0.719	**0.735**
FLAIR (Cropped)	**0.778**	0.690	0.755	**0.818**	0.565	**0.731**
T1 (Cropped)	0.731	**0.738**	0.727	**0.757**	0.645	**0.728**
T2 (Cropped)	**0.778**	0.732	0.740	**0.755**	0.690	**0.718**
T1ce-T1 (Cropped)	**0.895**	0.861	**0.764**	0.742	0.707	**0.723**

TABLE I
RESULTS COMPARING MTL MODELS ACROSS PREDICTION TASKS AND MR INPUT FORMAT.

Table 2 shows survival prediction results broken down by WHO 2016 glioma molecular subtype. Our survival models perform well on 1p/19q co-deleted tumors and offer some improvement for IDH1/2 wildtype gliomas. Our best MTL-embedding-based survival models outperform linear Cox proportional-hazards models trained on SCNA data alone, suggesting adding MR data to SCNA data improves survival prediction.

Input Modalities	1p/19q Co-deletion (C-index)		IDH1/2 Mutant, 1p/19q Intact (C-index)		IDH1/2 Wildtype (C-index)	
	MR	MR + SCNA	MR	MR + SCNA	MR	MR + SCNA
All (Whole Brain)	0.714	**1.000**	0.606	**0.727**	0.487	**0.521**
All (Cropped)	0.607	**0.964**	**0.742**	0.712	0.540	**0.548**
T1ce (Cropped)	**0.821**	0.786	0.576	**0.742**	**0.644**	0.571
FLAIR (Cropped)	0.607	**0.964**	0.636	**0.712**	0.527	**0.540**
T1 (Cropped)	0.643	**0.893**	0.606	**0.636**	0.535	**0.544**
T2 (Cropped)	**0.679**	0.500	**0.803**	0.697	0.562	**0.563**
T1ce-T1 (Cropped)	0.821	**0.857**	**0.803**	0.682	0.523	**0.552**
SCNA (PCA = 5)	0.929		0.667		0.512	

TABLE II
MTL SURVIVAL PERFORMANCE BROKEN UP OVER WHO 2016 GLIOMA SUBTYPES.

TUMOR RING ENHANCEMENT GUIDES IDH1/2 MUTATION PREDICTION

Figure 4. Our T1ce-based IDH1/2 MTL network appears to associate tumor ring enhancement with IDH1/2-wildtype tumors. Sample **A-B, E)** are IDH1/2-mutant glioma with ring enhancement misclassified as IDH1/2-wildtype tumors. Samples **C-D)** are IDH1/2-wildtype tumors with mild and no enhancement misclassified as IDH1/2-mutants. Integrated gradients shown in the images to the right of **E)** and **F)** show that this model puts emphasis on tumor ring enhancement.

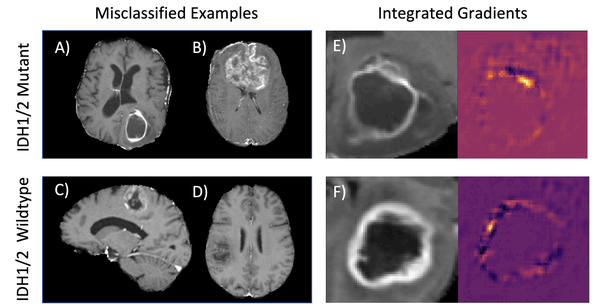
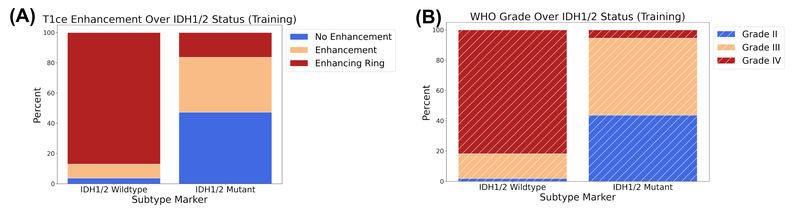


Figure 5. Tumor ring enhancement and grade correlate with IDH1/2 mutation status. The bar chart (A) shows correlation between tumor ring enhancement and IDH1/2-wildtype status (r=0.79, p=$10e^{-14}$) in the training set; the bar chart (B) also shows similar correlation between high tumor grade (WHO grade II/III vs. WHO Grade IV) and IDH1/2-wildtype status (r=0.74, p=$10e^{-11}$). The association of tumor ring enhancement with IDH1/2-wildtype tumors likely explains our model's errant predictions shown in Figure 4, and the association of tumor grade with IDH1/2-wildtype tumors may explain why the majority of IDH1/2-wildtype tumor show ring enhancement. Future experiments will control for tumor enhancement and grade, though sample size and class imbalance will present challenges.



SUMMARY

- MTL allows unlabeled MR data to contribute to glioma molecular subtype and survival prediction.
- When SCNA data is used in conjunction with MR data, results further improve.
- Tumor ring enhancement and grade are possible confounders in IDH1/2 mutation prediction.

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